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Beware of nonconvulsive seizures in prolonged disorders of consciousness: Long-term EEG monitoring is the key

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HIGHLIGHTS

- One third of long-term EEG monitoring (LTM) in prolonged disorders of consciousness patients showed epileptic discharges (EDs), either sporadic, rhythmic or periodic patterns.
- Nonconvulsive seizures (NCSz) were recorded in 12% of patients, of whom only two had a history of clinical seizures.
- LTM outperformed standard and repeated EEGs for detecting EDs and NCSz.

ABSTRACT

Objective: Evaluate the prevalence of epileptic seizures (ES) and epileptiform discharges (EDs) in patients with prolonged disorders of consciousness (DOC), and potential influence of amantadine on epilepsy.
Methods: We conducted a retrospective study in 34 patients hospitalized in a DOC care unit for prolonged DOC between 2012 and 2018, who received a long-term EEG monitoring (LTM). We reviewed the prevalence of ES, EDs and nonconvulsive seizures (NCSz), the type of DOC recovery treatment administered, and neurological outcome.
Results: LTM was more effective than standard EEGs in detecting EDs (32% vs 21% respectively). Moreover, 12% of the LTM showed NCSz. Among patients with EDs in LTM, 73% showed no EDs in standard EEG recordings, even when performed more than once. The presence of EDs and/or NCSz in LTM was significantly associated with the occurrence of remote clinical epileptic seizures ($p = 0.017$) but did not influence neurological outcome ($p = 1$). Amantadine was not associated with higher occurrence of EDs/NCSz or clinical seizures.
Conclusion: In our prolonged DOC population, LTM showed more pathological results (EDs and NCSz) than standard EEGs, which was significantly associated with remote clinical seizures.
Significance: The use of LTM might be advised to rule out NCSz in patients with prolonged DOC.

1. Introduction

Following severe brain injury leading to coma, patients may evolve towards a prolonged disorder of consciousness (DOC) (Giacino et al., 2018), including unresponsive wakefulness syndrome (UWS) (Laureys et al., 2010), or minimally conscious state (MCS) (Giacino et al., 2002).

Patients with DOC usually suffer from potentially widespread epileptogenic brain lesions and clinical seizures occur in as many as a quarter of those patients (Bagnato et al., 2013). Using transcranial magnetic stimulation (TMS), it is possible to demonstrate that patients with unresponsive wakefulness syndrome (UWS) have abnormal cortical excitability, compared to healthy subjects

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(Bagnato et al., 2012). Two studies conducted in prolonged DOC patients, using systematic standard EEG recordings, demonstrated a significantly higher risk of clinical seizure occurrence if epileptic discharges (EDs) were present, especially when EDs were periodic or bilateral (Bagnato et al., 2016; Pascarella et al., 2016). However, nonconvulsive seizures (NCSz) were not reported. It has also been shown that clinical seizures, but not the presence of EDs, have a negative impact on long-term outcome (Pascarella et al., 2016). The main limitation of those studies is the lack of long-term EEG monitoring (LTM). Moreover, the prevalence of seizures in DOC might be underestimated since the recognition of NCSz is particularly challenging in these unconscious and disabled patients, similarly to what has been demonstrated in critically ill patients in coma following acute brain injury (Claassen et al., 2004; Ruiz et al., 2017). Similarly, the prevalence of EDs including periodic and rhythmic patterns, associated with a higher risk of seizures (Claassen et al., 2004; Cormier et al., 2017; Hirsch, 2011; Ruiz et al., 2017; Struck et al., 2017), might also be underestimated with standard EEG. Still, as far as we are aware, the use of LTM in prolonged DOC patients is not a common practice.

Therefore, the aim of this study was to assess the prevalence of NCSz and EDs in patients with prolonged DOC, using LTM and compare it with standard EEG findings. We also sought to determine the association of these findings with outcome. We also assessed the potential influence of amantadine on the occurrence of EDs and NCSz, since amantadine is the most common treatment used for promoting DOC recovery and the only drug that showed class II evidence for promoting DOC recovery following a traumatic brain injury (Giacino et al., 2012; Thibaut et al., 2019). Nevertheless, to our knowledge only one study evaluated the seizure risk correlated to amantadine administration in this particular patients population so far and did not find an increased risk for seizure occurrence during treatment (Giacino et al., 2012).

2. Methods

2.1. Study design and sample

We conducted a retrospective study on all consecutive patients with prolonged DOC admitted to the DOC care unit in the William Lennox Neurological Hospital (WLNH) between January 2012 and December 2018, who received LTM (24-h), and standard (20-min) EEG for a subgroup of the population. The inclusion criteria for this study were: minimum age of 16 years, diagnosis of coma or prolonged (>28 days) DOC (either UWS or MCS) according to the Coma Recovery Scale-Revised (CRS-R), at least one LTM performed. Exclusion criteria were the presence of epilepsy before DOC onset, locked-in syndrome and akinetic mutism (Fig. 1). The diagnosis of akinetic mutism and locked-in syndrome were based on clinical (signs of consciousness despite an inability to produce motor and/or verbal response) and/or radiological findings (anatomical localization of brain injuries on descriptive MRI, FDG-PET scan findings).

The study was approved by the Ethics Committee of the WLNH. Written consents have been collected from the legal surrogates of the participants.

2.2. Clinical and neurophysiological assessments

The diagnosis of the subtype of DOC was based on the clinical evaluation of the multidisciplinary team (including neurologists, neuropsychologists, speech therapists and specialized nurses) and the CRS-R diagnosis at admission. For the purpose of this study, we considered the subtype of DOC at the moment of LTM recording and considered it as "unknown" when the closest CRS-R evaluation was performed more than 30 days apart from the recording. Outcome was considered at the moment of discharge from the unit, and defined by the CRS-R diagnosis, unless the patient died. The classification of DOC was the following: coma, UWS or MCS (Bodart et al., 2013; Bruno et al., 2012). We considered as "recovered" patients who showed a substantial clinical change (i.e. UWS patients who became MCS and MCS patients who recovered full consciousness) and as "unrecovered" DOC patients whose clinical diagnosis did not substantially change, comparing CRS-R diagnosis at admission and at discharge.

Neurophysiological evaluation of the patients staying in the DOC care unit was based on EEG recordings' review. Standard EEG and LTM were recorded using 19 or 23 electrodes placed according to the 10–20 international system, at the bedside, using a clinical grade amplifier (Micromed System, impedances < 5 kΩ, band-pass = 0.3–70 Hz, sampling rate = 256 Hz,). Concomitant video-recordings were obtained for standard EEGs. For LTM, video recordings were not available, thus clinical monitoring was performed by the medical staff and patients' families. For the purpose of this study, LTM recordings were all reviewed by an independent reader, certified in neurophysiology, and blinded to the clinical data (NG). We systematically recorded the presence or absence of reactivity, posterior dominant rhythm, sporadic epileptiform discharges, rhythmic or periodic discharges and NCSz, as defined by consensus criteria (Gaspard et al., 2014; Herman et al., 2015; Hirsch et al., 2013). Sporadic epileptiform discharges and all types of periodic or rhythmic discharges, were considered epileptiform discharges (EDs), except generalized rhythmic delta activity (GRDA) since it is not associated with seizures, either clinical or electrographic (Johnson and Kaplan, 2017; Kapinos et al., 2018; Schmitt, 2018). The subgroup of patients who underwent both types of recordings (standard EEG and LTM) were used for neurophysiological findings comparison.

We reviewed the patients' medical charts to collect demographic and clinical data from the DOC care unit stays, including etiology of brain injury and DOC, use of anti-seizure medication (ASM) or amantadine as a recovering therapy, occurrence of clinical seizure and neurophysiological findings during the acute phase preceding admission in the DOC unit. Clinical seizures and NCSz occurring within a period of seven days following the onset of the brain injury were considered as acute symptomatic seizures, whereas seizures occurring after seven days were considered as remote seizures (Beghi et al., 2010). Seizure "co-occurrence" with the administration of amantadine was defined as the occurrence of an epileptic seizure within a week after treatment administration or dose increase.

2.3. Statistical analysis

All the data could be retrieved from charts and all the LTM recordings could be reviewed, therefore there were no missing values before statistical analysis.

Descriptive statistics are used to summarize clinical and demographic characteristics of the sample. We investigated the association between gender, age group, etiology, DOC treatment, ASM administration (as prophylaxis or secondary prevention), EDs occurrence on standard EEG, acute symptomatic/remote seizure occurrence, and EDs occurrence on LTM on the whole population sample. Then, we determined both the association between gender, age group, etiology, DOC treatment, ASM prophylaxis administration, epileptiform discharge occurrence (on both LTM and standard EEG), acute symptomatic seizures and remote seizure occurrence, and between the listed variables plus remote seizure occurrence and outcome (i.e., recovered, unrecovered or deceased). Throughout these analyses, age was categorized according to the quartiles, and Fisher exact tests were used in case expected cell

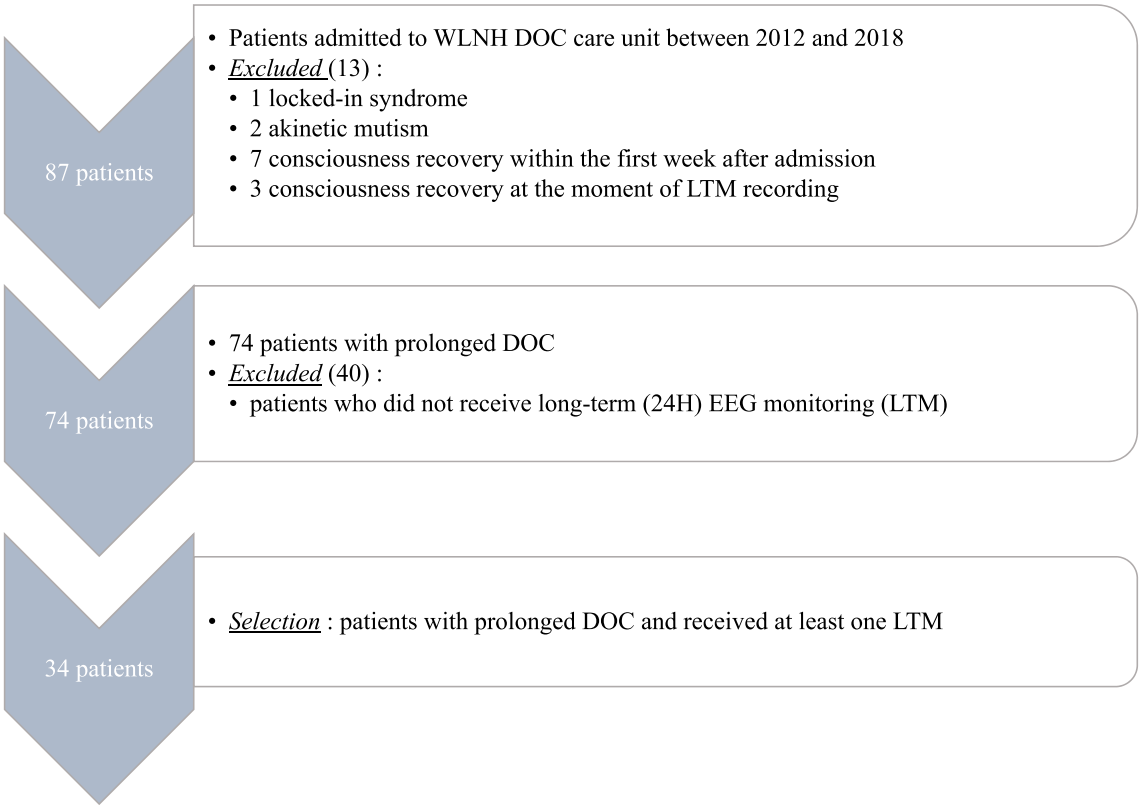

Fig. 1. Flow chart of the patients' selection. DOC: disorders of consciousness; WLNH: William Lennox Neurological Hospital.

counts were below 5, and chi-square tests if otherwise. The significance level was set at $p < 0.05$. All statistical procedures were run using R 4.0.0 (R Core, 2020)

3. Results

3.1. Patient selection and clinical features

The study population consisted of 34 patients, aged from 16 to 73 years (mean age 41) and with a slight male predominance (19 male, 15 female).

On admission in the DOC care unit of the WLNH, the DOC was diagnosed as follows: two patients (6% of the whole population included) in coma, 16 (47 %) in UWS and 16 in MCS, according to the CRS-R diagnosis. The mean duration between brain injury and admission to the DOC unit was 60 days (range 26–140). The causes of the DOC were traumatic brain injury (TBI) (38%), hemorrhagic (32%) or ischemic (6%) stroke, anoxic brain injury (21%) and CNS infection (3%). The mean duration of hospitalization was 240 days (range 26–461). The mean number of CRS-R performed per patient retrieved from medical charts was 3.5 (range 1–10).

3.2. Neurophysiological findings during the DOC care unit stay

3.2.1. Long-term (24 h) EEG monitoring (LTM) and demographic data

LTM was performed for re-assessment of indication of treatment with anti-seizure medication (ASM) (n = 17), suspicion of epilepsy/seizures (n = 10), the lack of recovery of consciousness after several months (n = 5) or as part of a clinical trial monitoring (n = 2). The mean number of LTM performed per patient was 2 (range 1–6). The mean duration of the DOC before the first LTM was 109 days (range 33–255). All of the LTM were suitable for systematic review.

At the moment of recording, 45% patients were in a UWS and 55% in a MCS, according to the closest CRS-R diagnosis (mean delay of 11 days, range 1–30).

A large majority of the recordings showed the presence of a posterior dominant rhythm (77%) and of reactivity (98%). A third of them (11/34) showed epileptiform, sporadic, periodic or rhythmic discharges, detailed as follows: 8/11 (73%) sporadic EDs (7 Focal ED, 1 Generalized ED), 3/11 (28%) Lateralized Rhythmic Delta Activity (LRDA), 1/11 (9%) Lateralized Periodic Discharges (LPDs). Three examples of rhythmic or periodic patterns are represented in Fig. 2. Four patients (12%) had NCSz, among whom only two had a history of clinical seizures (either acute symptomatic or remote seizure) prior to EEG recording (Fig. 3). Most patients (50%) with EDs in LTM had no EDs found on single or repeated standard EEG recordings. At the moment of LTM recording, 74% were receiving ASM, 40% amantadine and 25% of them presented at least one remote clinical seizure during their stay. The association between the presence of NCSz on LTM and the occurrence of remote clinical seizures was statistically significant ($p = 0.002$). We found evidence for a significant effect of the presence of EDs in LTM and the occurrence of remote clinical epileptic seizures ($p = 0.033$), whereas no statistically significant association between gender ($p = 1$), age group ($p = 0.668$), etiology ($p = 1$), DOC treatment ($p = 0.438$), ASM administration ($p = 0.692$), acute symptomatic seizure ($p = 1$) and remote seizure occurrence was found (Table 1).

3.2.2. Standard EEG recordings and demographic data

Standard EEG recordings were also performed on 24 of the total 34 LTM patients, mostly for treatment evaluation or suspected seizure. The mean number of standard EEG performed per patient was 3 (range 1–15). During the recordings, sensorial stimulations were performed (acoustic, tactile, nociceptive and photic) to assess

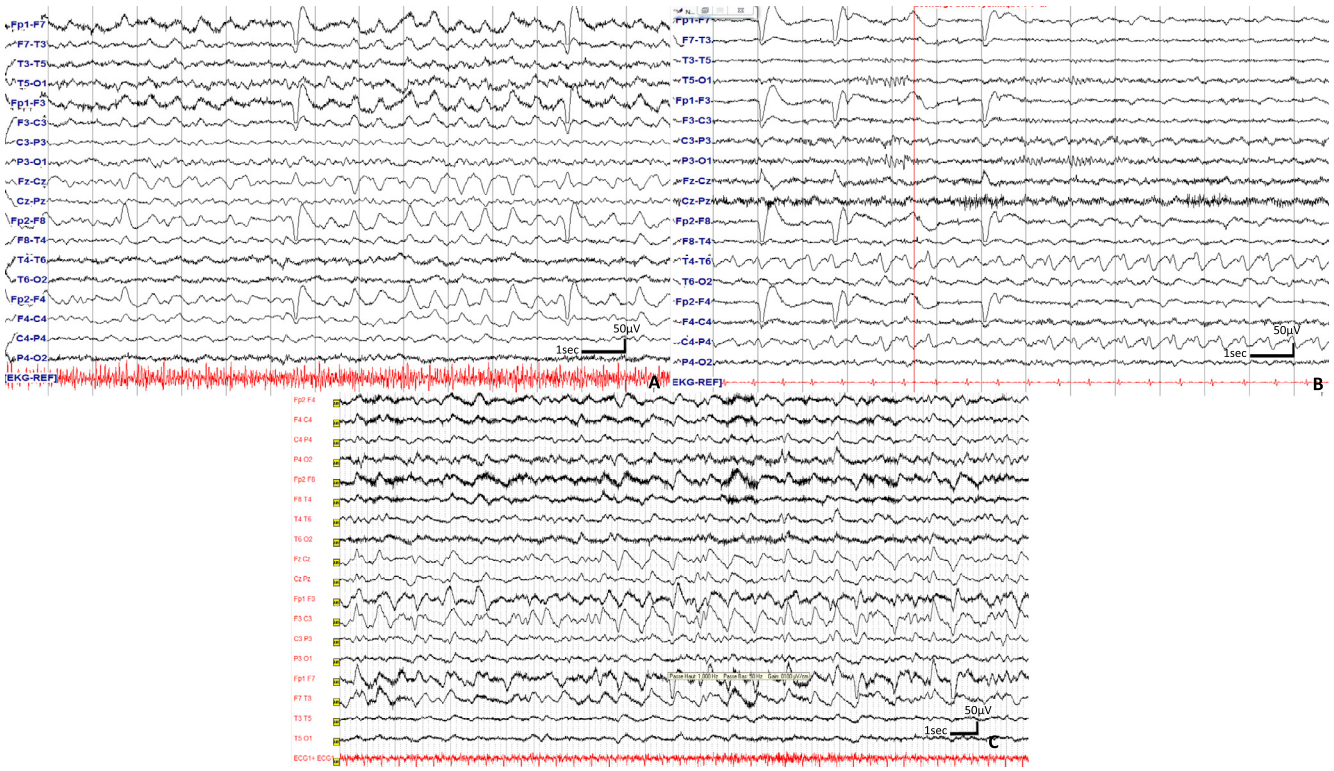

Fig. 2. Example of periodic and rhythmic discharges seen on long-term EEG monitoring (LTM) in patients with disorders of consciousness (DOC) (bipolar montage). A: Generalized rhythmic delta activity (GRDA), frontally-predominant recorded in a 27 year old man, 6 months after DOC onset; B: Lateralized periodic discharges (LPDs) recorded in a 16 year old woman, 4 months after DOC onset. Both had vascular lesions leading to DOC; C: Lateralized Rythmic Delta Activity (LRDA) recorded in a 47 year old woman, 4 months after DOC onset due to hemorrhagic lesions.

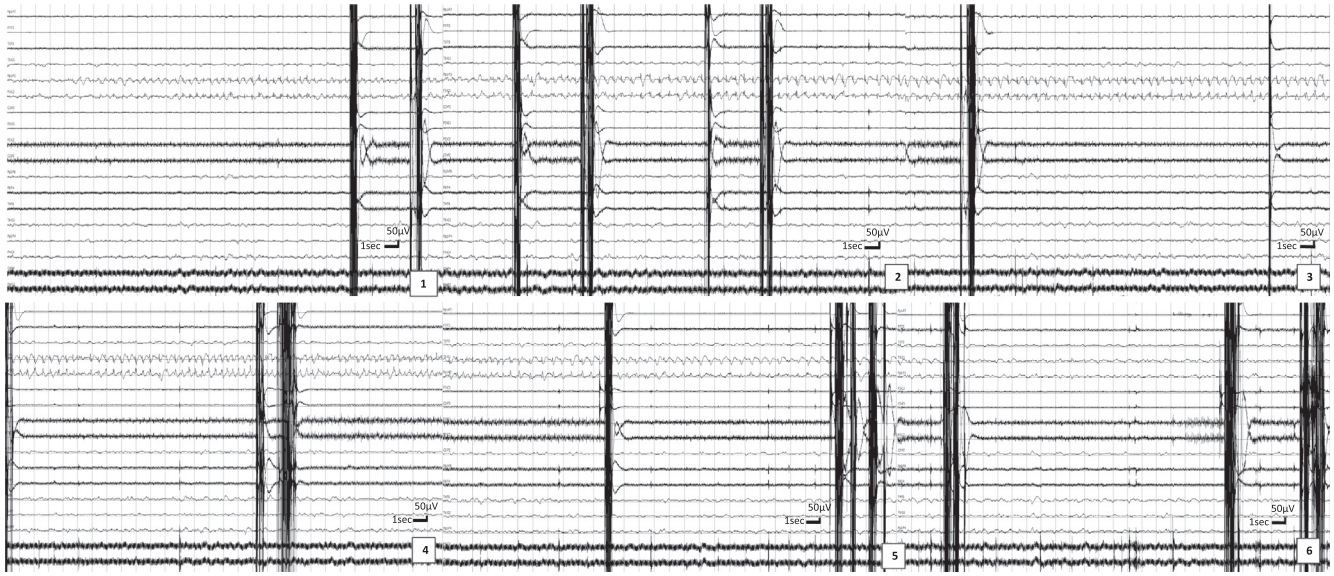

Fig. 3. Example of a nonconvulsive seizure recorded in long-term EEG monitoring (LTM). 1 to 6: Left frontal nonconvulsive seizure recorded in a 18 year old man, 4 months after disorder of consciousness (DOC) onset consecutive of a severe traumatic brain injury.

the reactivity. The mean duration of the DOC before the first standard EEG recording was 126 days (range 12–337). Only 21% of the recordings showed EDs, categorized as follows: 80% (4/5) focal EDs and 40% (2/5) LRDA. Only one patient had the same EDs in both LTM and standard EEG (sporadic EDs). All the other recordings were discordant (mostly pathological LTM with no EDs found on standard EEGs, 8/11). At the moment of recording, 61% of the patients were treated with ASM, 20% were treated with amantadine and two of the patients who showed EDs on standard EEG (40%) had a clinical remote seizure during their stay (p = 0.590). Thirty-two percent of patients who received a standard EEG recording were in a UWS at the moment of recording and 68% in a MCS. The mean time between CRS-R diagnosis and standard EEG recording was 6 days (range 1–20).

Table 1
Demographical and clinical findings of the whole population included (n = 34), comparing patients with and without EDs on LTM.

Variable	N (total = 34)	DOC patients with EDs in LTM (n = 11)	DOC patients without EDs in LTM (n = 23)	*p*-value
Age (mean +/- SD)	40 ± 9.6	39.3 ± 8.6	40.2 ± 9.2	0.581
Gender				0.715
Male	19 (56%)	7 (64%)	12 (52%)	
Female	15 (44%)	4 (36%)	11 (48%)	
Etiology				0.712
TBI	13 (38%)	5 (45%)	8 (35%)	
Vascular	13 (38%)	5 (45%)	8 (35%)	
Anoxic	7 (21%)	1 (9%)	6 (26%)	
Infectious	1 (3%)	0	1 (4%)	
ASM	25 (74%)	8 (72%)	18 (78%)	0.213
DOC treatment (amantadine)	16 (47%)	5 (45%)	11 (48%)	1
ASS	9 (26%)	2 (18%)	7 (30%)	0.682
Remote ES	9 (26%)	5 (45%)	4 (15%)	0.033
EDs on standard EEG recordings	5 (12.5%)	3 (23%)	2 (7%)	0.299

Legend: EDs = Epileptiform Discharges; LTM = Long-term EEG Monitoring; TBI = Traumatic Brain Injury; DOC = Disorder of Consciousness; ASM = Anti-seizure medication; ASS = acute symptomatic seizure; ES = Epileptic Seizure; EEG = Electroencephalogram.

3.3. Seizure characteristics and management

A total of 16 patients (47%) suffered from seizures (either acute symptomatic or remote, clinical or electrographic). Nine patients (26%) had acute symptomatic seizures and 9 had remote clinical seizures during their stay at the DOC care unit, among whom only two (5%) experienced both types of seizures. Among patients with remote clinical seizures, TBI (4/9) and lesions were predominant, followed by vascular (3/9, only hemorrhagic) and anoxic lesions (2/9). At the time of epileptic seizures occurrence, 45% were in a UWS and 55% in a MCS, according to the closest CRS-R performed. Five (55%) of the patients who experienced remote epileptic seizures had EDs on LTM. Five patients (5/11, 55%) were treated with amantadine when EDs were found in LTM, among whom 4 experienced remote seizures (half nonconvulsive), despite ASM administered to all of them.

ASM was administered to more than half of the population (n = 23). The reason for ASM administration was whether suspected or proven seizures (52%), anti-seizure prophylaxis (35%), Lance-Adams syndrome (9%), or previous EEG abnormalities (4%). Patients received monotherapy (64%), dual therapy (25%) or therapy with three drugs (11%).

3.4. Management of DOC

Approximately half of the patients (17/34) received amantadine, a treatment aimed at promoting recovery of consciousness. Out of 17 patients treated with amantadine, 5 patients (29%) had a history of acute symptomatic seizures, and 5 patients (29%) experienced seizures after amantadine onset. Amantadine was reduced or discontinued for 2 patients, due to seizure occurrence within a week after amantadine treatment initiation. However, there was no statistical evidence for an association between amantadine administration and the occurrence of EDs (in standard EEGs or LTM) (p = 1) nor the occurrence of remote epileptic seizures (p = 0.438).

3.5. Neurological outcome

The neurological outcome was assessed after a mean hospitalization duration of 240 days (range 26–461) and mean time from brain injury of 300 days (range 83–514). A total of 22 patients (65%) recovered, 11 (32%) remained in a DOC (UWS/MCS with no significant clinical improvement comparing with the DOC at admission) and 1 (3%) patient died. Demographic and clinical data are described in Table 2. There was no significant gender differences between groups, neither clear differences in etiology or age. We did not find a significant association between the administration of amantadine, ASM, EDs, acute symptomatic or remote epileptic seizure occurrence and outcome. Moreover, the subtype of EDs found on LTM did not have a significant effect on the clinical outcome.

Table 2
Outcome: demographic and clinical data differences between the subgroups "recovered" and "unrecovered" (including deceased).

Clinical feature	Recovered	Unrecovered regroup	*p*-value
TOTAL POPULATION: n = 34	n = 22	n = 12	
Gender			1
Male	16 (55%)	6 (54.5%)	
Female	13 (45%)	5(45.5%)	
Age (mean +/- SD)	39 +/- 17	47 +/-16	0.370
Etiology			0.448
TBI	10 (45%)	3 (25%)	
Vascular	9 (41%)	4 (33%)	
Hemorrhage	7 (33%)	4 (33%)	
Ischemia	2 (9%)	0	
Anoxia	2 (9%)	5 (42%)	
Infection	1 (5%)	0	
DOC treatment (amantadine) (n = 17)	10 (45%)	7(58%)	0.464
ASS (n = 9)	4 (18%)	5 (42%)	0.110
Remote ES (n = 9)	7 (33%)	2 (17%)	0.682
Standard EEG (n = 24)	n = 17	n = 7	
EDs presence			1
EDs present (n = 5)	3 (18%)	2 (29%)	
EDs absent (n = 19)	14 (82%)	5 (71%)	
LTM (n = 34)			
EDs presence			1
EDs present (n = 11)	8 (36%)	3(25%)	
EDs absent (n = 23)	14(64%)	9 (75%)	
EDs subtype on LTM			1
LRDA (n = 4)	3(14%)	1 (8%)	1
LPD (n = 1)	1 (4%)	0	1
Sporadic EDs (n = 9)	7 (32%)	2 (17%)	1
NCSz on LTM (n = 4)	3 (9%)	1 (8%)	1

Legend: TBI = Traumatic Brain Injury; DOC = Disorder of Consciousness; ASS = Acute Symptomatic Seizures; ES = Epileptic Seizures; LTM = Long-term EEG monitoring; EDs = epileptiform discharges; LRDA = Lateralized Rhythmic Delta Activity; LPDs = Lateralized Periodic Discharges; NCSz = Non-Convulsive Seizure.

4. Discussion

4.1. Long-term EEG monitoring in DOC

The use of EEG monitoring in critically ill patients in the Intensive Care Unit is largely supported by studies showing high propor-

tions of nonconvulsive seizures or nonconvulsive status epilepticus (Herman et al., 2015; Punia et al., 2015; Ruiz et al., 2017; Struck et al., 2017). During the chronic management of DOC, performing LTM is not a common practice. Nevertheless, as suggested in previous studies, epileptic seizures are difficult to identify in these non-collaborative patients (e.g., inability to report non-motor seizure symptoms, difficulty to identify a decrease in the level of consciousness in patients with already impaired consciousness). It is also known that the sensitivity of the EEG increases with the duration of recording (Pascarella et al., 2016). Our results show that only half of the population admitted to the DOC care unit was monitored, mostly guided by the need of a treatment reevaluation or suspected epileptic seizures, which can be considered as a strong selection bias. Interestingly, LTM showed pathological results in a third of the patients tested (11/34). Sporadic EDs were more represented than rhythmic/periodic patterns (73 and 37%, respectively). Moreover, nonconvulsive seizures were identified in 12% of the recordings (4/34 patients) and for half of these patients, clinical seizures had never been identified before. Furthermore, LTM showed a higher occurrence of EDs than standard EEGs (32% vs 21%), and 73% of the patients with pathological LTM had no EDs on repeated standard EEGs. This reproduces classical findings of in critically ill patients, showing that the sensitivity of EEG increases with duration.

To our knowledge it is the first report of NCSz in the prolonged DOC population, probably because previous series did not use LTM (Bagnato et al., 2016, 2015, 2013; Pascarella et al., 2016). The higher yield of abnormal results, in comparison with standard EEGs, suggests that LTM should be more widely used in DOC populations, since it might be critical for anti-seizure medication management. Indeed, we found a strong and statistically relevant association between the occurrence of EDs or NCSz with the occurrence of remote clinical epileptic seizures ($p = 0.017$ and $p = 0.002$ respectively).

4.2. Epilepsy as a neurological outcome predictor

Animal (Avdic et al., 2018; Kršek et al., 2001) and human (Bagnato et al., 2015; Pascarella et al., 2016; Young and Claassen, 2010) studies bring strong arguments to support that NCSz or status epilepticus have deleterious effects on the neurological outcome. It was also shown that patients in acute phase of a coma have poorer outcomes when seizures occurred (Hesdorffer et al., 2009). In the prolonged DOC population, Pascarella *et al.* (Pascarella et al., 2016) showed that the presence of interictal epileptiform discharges correlate with worse consciousness outcome and that the majority of patients with periodic EDs experienced seizures (73%). Bagnato *et al.* (Bagnato et al., 2016) found an association between the presence of EDs on admission and the occurrence of seizures in the following three months (11% without EDs and 45% with EDs). Moreover, the risk of seizure occurrence was even higher if the EDs were bilateral (8 times higher than patients without EDs and 3.5 times higher than patients with unilateral EDs). In the present series, we found similar occurrence of epileptic remote seizures (25%) in prolonged DOC patients when compared to previous series (Bagnato et al., 2016, 2013; Pascarella et al., 2016). Nevertheless, we did not find a statistically significant association between the presence of EDs, their subtype nor the occurrence of ES or NCSz and outcome worsening. This could be due to the small sample studied and the retrospective nature of the study with the risk of selection bias. Moreover, adjustments in ASM administration were made according to the LTM results, which could have improved the final outcome. Therefore, further prospective studies using systematic LTM on DOC patients are needed.

4.3. Seizure occurrence and DOC treatment

Amantadine is the most commonly used drug for promoting consciousness recovery in patients with DOC. In our population, amantadine was delivered to half (50%) of the patients. A previous history of seizures was not considered as a contraindication, but we observed that such patients were slightly less likely to be treated with amantadine. This is possibly due to empirical fear of aggravating epilepsy, even in the absence of supporting evidence. Previous studies showed that amantadine administration (up to 400 mg/day) was not associated with higher seizure occurrence when compared to placebo in DOC patients secondary to traumatic brain injury, and could decrease cortical excitability at low doses (50–100 mg) (Barra et al., 2019; Giacino et al., 2012; Reis et al., 2006). In the present series, we did not find a statistically significant association between amantadine administration and the occurrence of EDs or remote epileptic seizures. In our population, 69% of patients treated with amantadine showed no seizure occurrence or increase due to amantadine administration. For the remaining 31% of patients treated, seizures were generally considered as unrelated to amantadine treatment, although it was difficult to retrieve more precise information from the medical charts due to the retrospective nature of the study. Prospective controlled pharmaceutical trials should be conducted to evaluate the definite impact of amantadine on seizure occurrence in prolonged DOC patients.

4.4. Limitations

This retrospective study has several limitations. Firstly, there is a selection bias: patients monitored with LTM were selected based upon suspicion or proven occurrence of epileptic seizures, or the need for a treatment. Most of the patients monitored were already treated with ASM which could lead to EDs/NCSz underestimation. Secondly, the patient sample was relatively small, thus resulting in the use of conservative statistical tests. For the Fisher exact test, we did not adjust p-values for multiple testing, as our aim was to explore first indications of the associations between variables. We further note that statistical methods such as the Fisher exact test do not allow controlling for potential confounding variables. Finally, the retrospective nature of the study precludes accurate data retrieval. This was the case for pre-DOC care unit EEG findings, seizure description, etc. It was also the case for details on remote seizures, especially regarding the relation to amantadine treatment. Importantly, the neurological status was considered unknown when the delay between routine CRS-R evaluation and LTM was too long (exceeding 30 days), leading to the exclusion of patients from statistical analysis. Therefore, additional prospective multicentric studies are needed to confirm our findings.

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.

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