Below is the unedited draft of the article that has been accepted for publication
(© Archives of Physical Medicine and Rehabilitation, 2017, V. 98., P. 665-672.)

Changes in standard EEG parallel consciousness improvement in patients with unresponsive wakefulness syndrome

Sergio Bagnato[1], Cristina Boccagni[1], Caterina Prestandrea[1], Alexander A. Fingelkurts[2], Andrew A. Fingelkurts[2], and Giuseppe Galardi[1]

[1)] Unit of Neurophysiology and Unit for Severe Acquired Brain Injuries, Rehabilitation Department, Fondazione Istituto Giuseppe Giglio, Cefalù (PA), Italy.
[2)] BM-Science – Brain and Mind Technologies Research Centre, Espoo, Finland.

Abstract

Objective: To identify changes in the standard electroencephalograms (EEGs) of patients with unresponsive wakefulness syndrome (UWS) who did or did not recover consciousness 6 months after admission to a rehabilitation department. ***Design***: Prospective cohort study. ***Setting***: Unit for Severe Acquired Brain Injuries. ***Participants***: Twenty-eight consecutive patients with UWS. ***Interventions***: Not applicable. ***Main Outcome Measures***: EEG amplitude (reduced or normal), dominant frequency (alpha, theta, or delta), and reactivity (absent or present) were scored at admission and 6 months later. The cumulative amplitude-frequency-reactivity (AFR) score was evaluated. Clinical assessments were made with the Coma Recovery Scale-Revised (CRS-R). ***Results***: Sixteen of the 28 patients with UWS recovered consciousness after 6 months. EEG improvements occurred in 87.5% patients with consciousness recovery and 16.7% patients without consciousness recovery. Improvements in EEG dominant frequency (from theta to alpha band or from delta to theta band), reappearance of EEG reactivity, and AFR score increase (p values < 0.01) differentiated patients with from those without consciousness improvement. Six months after admission for rehabilitation, patients with EEG improvements showed higher CRS-R scores compared to patients without EEG changes (p < 0.01). ***Conclusions***: Most patients who emerge from UWS demonstrate improvement in basic EEG characteristics over time. EEG changes in patients with UWS may aid in the timely recognition of patients transitioning into a minimally conscious state.

Key words:
1) Vegetative state.
2) Prognosis.
3) EEG amplitude.
4) EEG frequency.
5) EEG reactivity.

List of abbreviations:
AFR, amplitude-frequency-reactivity; CRS-R, Coma Recovery Scale-Revised; ECG, electrocardiogram; EEG, electroencephalogram; E-MCS, emergence from minimally conscious state; MCS, minimally conscious state; TBI, traumatic brain injury; UWS, unresponsive wakefulness syndrome.

Introduction

As a result of a severe brain injury, the organization of electrical brain activity is disrupted in patients with unresponsive wakefulness syndrome (UWS, formerly known as the vegetative state).[1] UWS is a clinical condition in which patients lose awareness of self and the external world, resulting in severe impairment of consciousness.[2,3] Several studies showed abnormalities in the standard electroencephalograms (EEGs) of patients with UWS,[4-10] with these abnormalities often being related to the patient's outcome.[4-6,9] In particular, abnormalities in EEG amplitude, frequency, and reactivity have been reported. In a population of 59 patients with UWS, a reduced EEG background amplitude (< 20 μV) was observed in 35.6% of cases.[9] Reduced EEG amplitude was more common in patients with UWS than in patients in a minimally conscious state (MCS) and was correlated with poor outcomes.[9] Studies using EEG visual analysis found that the resting dominant background frequency in patients with UWS was always in the range of theta or delta bands, whereas it was never in the alpha band.[5,9] Conversely, patients in a MCS never showed a dominant delta band, but displayed a dominant alpha band in 36.2% of cases.[9] Finally, EEG reactivity to stimuli has been correlated with level of consciousness and patient outcomes.[6,9] EEG reactivity is more likely to be seen in patients in a MCS compared to those with UWS.[9] Moreover, the presence of EEG reactivity predicts good improvements in the level of consciousness over time.[6,9]

We have proposed that the recovery from UWS may occur through plastic changes that restore brain connectivity and functions.[11,12] EEG potentially represents a powerful tool to follow these changes over time. Our hypothesis is that changes in EEG amplitude, frequency, and reactivity may parallel improvements in the level of consciousness. To examine this possibility, we evaluated how EEG amplitude, frequency, and reactivity changed in patients with UWS who did or did not recover consciousness 6 months after admission to a rehabilitation department.

Methods

Patients

This prospective study was conducted on 28 consecutive patients with UWS (20 males and 8 females; mean age: 42.3 ± 14.9 years) who were admitted to our Unit for Severe Acquired Brain Injuries between July 2011 and September 2015 (Table 1). All patients had been admitted for intensive rehabilitation after an acute brain injury (mean time from brain injury to admission: 55 ± 35.4 days). All patients who fulfilled the following criteria were included in the study: 1) diagnosis of UWS upon admission to our department after an acute brain injury; 2) age between 18 and 70 years; and 3) hospitalization in our department for at least 6 consecutive months. Among the 35 patients who fulfilled the first two inclusion criteria, 7 patients were excluded because they died (4 patients because of sepsis, 1 patient because of respiratory failure) or were transferred to another hospital (2 patients) before the end of the evaluation period. Patients with a previous history of epilepsy, traumatic brain injury (TBI), stroke, cerebral hypoxia, neurodegenerative disease, or infection of the central nervous system were not included. The ethics committee of Fondazione Istituto Giuseppe Giglio (Cefalù, Italy) approved this study. Patients' legal guardians gave their written informed consent to all procedures.

Table 1. Patient demographic, clinical, and EEG details at admission.

Patient	Sex	Age (y)	Time since brain injury (d)	Etiology	CRS-R score	CT/MRI data	Drugs affecting consciousness (mg/day)	EEG			
								A	F	R	AFR score
Patients with consciousness improvement											
1	M	65	63	TBI	4	Left frontal ischemia	None	2	2	2	6
2	M	33	53	TBI	7	Left fronto-parietal SaH, EH with brainstem compression	BCF 60; CMZ 400	2	1	1	4
3	F	38	39	TBI	2	Right hemispheric SdH, left temporal CC, DAI	BCF 45	2	2	1	5
4	M	19	101	TBI	7	Right fronto-parietal SdH	BCF 100; LEV 1000; LCS 100	2	2	2	6
5	F	56	54	Cerebral hypoxia	5	Cerebral edema	None	1	2	1	4
6	M	21	24	TBI	5	Cerebral edema, DAI	BCF 20; CMZ 800	2	2	1	5
7	M	25	26	TBI	6	Left fronto-temporal SdH, brain edema	CMZ 800	2	2	2	6
8	M	46	26	ACA aneurysm rupture	4	SaH, cerebral edema	CMZ 800	1	1	1	3
9	F	46	85	Neurosurgery for meningioma	6	Cerebral edema and multiple ischemic lesions	None	2	2	1	5
10	M	23	24	TBI	4	Left temporo-occipital and bilateral frontal SaH	None	2	2	1	5
11	F	63	23	Cavernous malformation rupture	3	SaH with hydrocephalus	CMZ 800; LEV 1000	2	2	1	5
12	M	65	31	TBI	6	Right hemispheric EH	None	2	2	1	5
13	M	38	27	TBI	6	DAI	None	2	2	2	6
14	M	56	91	ACA aneurysm rupture	3	SaH with hydrocephalus	PH, 300	2	1	1	4
15	M	22	35	TBI	5	Cerebral edema and DAI	None	1	2	2	5
16	M	54	112	TBI	6	Multiple areas of cortical damage	BCF 30; LEV 1000	2	2	1	5
Patients without consciousness improvement											
1	F	43	63	Cerebral hypoxia	5	Cerebral edema	None	1	1	1	3
2	M	45	53	TBI	4	Bilateral SaH, multiple CC	None	2	2	1	5
3	M	50	60	Cerebral hypoxia	4	Cerebral edema	BCF 100	1	1	1	3
4	M	40	42	TBI	4	Right hemispheric SdH	LEV 1500	2	2	1	5
5	M	46	41	Cerebral hypoxia	2	Signs of cortical and subcortical hypoxic damage	LEV 1000	1	1	1	3
6	M	50	176	Encephalitis	6	Multiple areas of cortical and subcortical damage	BCF 60; PB 100	1	2	1	4
7	F	30	29	Cerebral hypoxia	5	Signs of cortical and subcortical hypoxic damage	None	1	1	1	3
8	F	24	89	TBI	6	DAI	None	1	1	1	3
9	M	60	17	Cerebral hypoxia	3	Signs of subcortical hypoxic damage	LEV 1000	1	1	1	3
10	F	55	58	Cerebral hypoxia	5	Signs of cortical and subcortical hypoxic damage	None	1	1	1	3
11	M	53	73	TBI	4	Bilateral SaH, bilateral frontal EH	PB 100	2	2	1	5
12	M	18	25	TBI	4	Bilateral SaH	None	1	2	1	4

EEG data are reported in four columns. In column A, 1 indicates reduced amplitude, and 2 indicates normal amplitude. In column F, 1 indicates delta frequency, and 2 indicates theta frequency. In column R, 1 indicates absent reactivity, and 2 indicates present reactivity. Column AFR score reports the sum of columns A, F, and R. Etiology and CT/MRI data abbreviations: ACA, anterior communicating artery; CC, cortical contusion; DAI, diffuse axonal injury; EH, epidural hematoma; SaH, subarachnoid hemorrhage; SdH, subdural hematoma; TBI, traumatic brain injury. CRS-R, Coma Recovery Scale Revised. Drugs affecting consciousness abbreviations: BCF, baclofen; CMZ, carbamazepine; LCS, lacosamide; LEV, levetiracetam; PB, phenobarbital; PH, phenytoin. EEG abbreviations: A, amplitude; F, frequency; R, reactivity; AFR, amplitude-frequency-reactivity.

Clinical and EEG evaluations

The first clinical assessment was made over 3 consecutive days (at admission and on the following 2 days) by neurologists who were trained in the evaluation of patients with disorders of consciousness. All patients underwent a standard neurological examination and assessment by the Coma Recovery Scale Revised (CRS-R), which provides standardized criteria for the diagnosis of UWS, MCS, and emergence from MCS (E-MCS).[13,14] To reduce the risk of misdiagnosis, a diagnosis of UWS was accepted if confirmed at all three evaluation times. The total CRS-R score ranges from 0 (comatose state) to 23 (E-MCS). If a discrepancy was found among the CRS-R scores on the 3 days, then we used the score obtained on the day that EEG was performed. During rehabilitation, patients were assessed with the CRS-R weekly, and the same neurologist repeated the 3-day clinical assessment 6 months after admission. Clinical evaluations were performed at the patient's bedside at admission and at the patient's bedside or wheelchair after 6 months.

Baseline EEGs were recorded at the patient's bedside in the morning within 2 days after admission. EEGs utilized 20 electrodes, which were placed according to the 10–20 system (O1, O2, Oz, P3, P4, Pz, T5, T6, C3, C4, Cz, T3, T4, F3, F4, Fz, F7, F8, Fp1, and Fp2) with a standard procedure (eyes closed, at least 30 minutes, impedances <5 kΩ, band-pass = 0.5–70 Hz, notch filter ON, sampling rate = 256 Hz, longitudinal bipolar montage, cephalic reference). Oculograms to monitor ocular movements and electrocardiograms (ECGs) to monitor ECG artifacts were available for all recordings. EEG recording started if patients had their eyes open. Eyelids were closed by hand until the end of registration.

EEG recordings were analyzed by electroencephalographers who were blinded to clinical data and CRS-R scores. EEG amplitude, frequency, and reactivity were visually assessed according to previous studies.[9,10] Amplitude was defined as reduced (amplitude < 20 μV in >10 channels during the entire recording) or normal (amplitude > 20 μV). Dominant frequency band was defined as delta, theta, or alpha, based on the most common frequency band in more than half of the channels. EEG reactivity was evaluated by a forced eye opening (15 seconds) repeated three times at intervals of approximately 5 minutes. Reactivity was considered present when changes in frequency (increase or slowing) or amplitude (increase or reduction) were detected during opening of the eyes in at least one of the trials. If no changes were detected in any of the three trials, then reactivity was considered absent.

On the basis of the EEG amplitude, frequency, and reactivity scores, the overall amplitude-frequency-reactivity (AFR) score was calculated. The AFR score is an EEG grading system that allows more delineated descriptions of outcome than data on amplitude, frequency, and reactivity considered alone.[9] Amplitude was scored as 1 if reduced or 2 if normal. Dominant frequency band was scored as 1 for delta, 2 for theta, or 3 for alpha. Reactivity to stimuli was scored as 1 if absent or 2 if present.[9] The AFR score comprises the sum of the amplitude, frequency, and reactivity scores, and it ranges from 3 (reduced amplitude, delta frequency, and absent reactivity) to 7 (normal amplitude, alpha frequency, and present reactivity).

Statistical analyses

Using the CRS-R data after 6 months, we divided patients into two groups: patients with consciousness improvement (i.e., who improved into a MCS or E-MCS) and patients without consciousness improvement (i.e., who still had UWS). Differences in patient demographic and clinical data were assessed by Student's t-test or Mann–Whitney U test. Using Fisher's exact test, we compared baseline EEG amplitude, frequency, and reactivity and their changes 6 months later between patients with or without consciousness improvement. Using the Mann–Whitney U test, we compared baseline AFR scores and changes 6 months later between patients with or without consciousness improvement. Moreover, we divided patients into two groups based on EEG changes: patients with or without AFR score changes. Using the Mann–Whitney U test, we compared patients with and without AFR score changes in terms of their CRS-R scores after 6 months and their CRS-R score changes from admission to 6 months. For all analyses, a p value <0.05 (one-tailed or two-tailed, as appropriate) was considered statistically significant.

Results

Demographic and clinical data

Among the 28 patients included in the study, 16 patients showed improved levels of consciousness after 6 months (8 patients to MCS and 8 patients to E-MCS), whereas 12 patients still had UWS (Table 2). Patients with or without consciousness improvement did not differ in age (41.9±16.7 and 42.8±12.8 years, respectively; p=0.9), days between brain injury and admission (50.9±30.6 and 60.5±41.8 days, respectively; p=0.5), or CRS-R score at admission (4.9±1.5 and 4.3±1.2 points, respectively; U=70.5; p=0.2). The number of hypoxic brain injury cases was lower among patients with improvement compared to those without consciousness improvement (p=0.03).

Table 2. Patient clinical and EEG details after 6 months.

Patient	Diagnosis	CRS-R score	Drugs affecting consciousness (mg/day)	EEG			
				A	F	R	AFR score
Patients with consciousness improvement							
1	E-MCS	23	None	2	3	2	7
2	MCS	9	None	2	2	1	5
3	MCS	16	BCF 75	2	3	2	7
4	MCS	10	LEV 2000	2	2	2	6
5	MCS	7	BCF 30	2	2	2	6
6	E-MCS	23	CMZ 800	2	3	2	7
7	E-MCS	21	ALZ 0.5; CMZ 800	2	3	2	7
8	MCS	10	BCF 75; CMZ 600	1	1	1	3
9	MCS	18	None	2	2	2	6
10	E-MCS	23	None	2	2	2	6
11	MCS	8	LEV 1000	2	2	2	6
12	E-MCS	22	CMZ 800; ALZ 0.25	2	2	2	6
13	E-MCS	23	TMD 200	2	3	2	7
14	MCS	8	PB, 200; PH, 300	2	2	2	6
15	E-MCS	23	None	2	3	2	7
16	E-MCS	19	LEV 1000	2	3	2	7
Patients without consciousness improvement							
1	UWS	6	BCF 75	1	1	1	3
2	UWS	5	None	2	2	1	5
3	UWS	6	BCF 100	1	1	1	3
4	UWS	6	BCF 45; LEV 1500	2	2	1	5
5	UWS	3	LEV 1500	1	1	1	3
6	UWS	4	BCF 60; TMD 150	1	2	1	4
7	UWS	5	None	1	1	1	3
8	UWS	6	LEV 1000; PB 100	1	1	1	3
9	UWS	5	LEV 1000; TMD 150	2	2	1	5
10	UWS	6	TMD 150	1	1	1	3
11	UWS	5	BCF 50; PB 15; TMD 100	2	2	1	5
12	UWS	5	None	2	2	1	5

EEG data are reported in four columns. In column A, 1 indicates reduced amplitude, and 2 indicates normal amplitude. In column F, 1 indicates delta frequency, 2 indicates theta frequency, and 3 indicates alpha frequency. In column R, 1 indicates absent reactivity, and 2 indicates present reactivity. Column AFR score reports the sum of columns A, F, and R. Diagnosis abbreviations: E-MCS, emergence from minimally conscious state; MCS, minimally conscious state; UWS, unresponsive wakefulness syndrome. EEG abbreviations: A, amplitude; F, frequency; R, reactivity; AFR, amplitude-frequency-reactivity. Drugs affecting consciousness abbreviations: ALZ, alprazolam; BCF, baclofen; CMZ, carbamazepine; LEV, levetiracetam; PB, phenobarbital; PH, phenytoin; TMD, tramadol.

Baseline EEG in patients with or without consciousness improvement

Among the 16 patients with consciousness improvement, the number of cases with reduced EEG amplitude was lower, and the number of cases with normal amplitude was higher, compared to patients without improvement (Table 3A). Patients with consciousness improvement had a lower number of cases with dominant delta band and a higher number of cases with dominant theta band compared to patients without improvement (Table 3A). Five of the 16 patients with consciousness improvement showed EEG reactivity, which was absent in all patients without improvement (Table 3A). The overall baseline AFR score was higher in patients with compared to patients without consciousness improvement after 6 months (U=32.5; $p<0.01$).

EEG changes after 6 months in patients with or without consciousness improvement

After 6 months, patients with or without consciousness improvement did not show different changes in the EEG background amplitude (Table 3B). Only 2 patients in each group showed an improvement from reduced to normal EEG amplitude, accounting for 12.5% of patients with and 16.7% of patients without consciousness improvement.

Improvement in the dominant EEG frequency was more frequent in patients with compared to patients without consciousness improvement (Table 3B). Nine of the 16 patients with consciousness improvement (56.3%) showed a change in the dominant EEG frequency from the theta to alpha band (7 patients) or from the delta to theta band (2 patients) after 6 months. Conversely, only one of the 12 patients without consciousness improvement (8.3%) showed a change in the dominant frequency from the delta to theta band.

Only patients with consciousness improvement showed the reappearance of EEG reactivity after 6 months (Table 3B). Nine of the 16 patients with consciousness improvement, corresponding to 81.9% of patients who did not show EEG reactivity at admission, had reappearance of EEG reactivity at the 6-month follow-up. On the contrary, none of the patients without consciousness improvement showed reappearance of EEG reactivity.

The AFR score increase was greater in patients with compared to patients without consciousness improvement after 6 months (U=29; $p<0.01$) (Figure 1). Fourteen of the 16 patients with consciousness improvement (87.5%) showed an increase in the AFR score, including eight patients with a one-point increase and six patients with a two-point increase. On the other hand, the AFR score increased in only two of the 12 patients without consciousness improvement (16.7%), with 1 patient each showing a one- or two-point increase.

Table 3. EEG findings at admission and after 6 months.

A	EEG at admission						
	Amplitude		*Frequency*		*Reactivity*		**Total**
	Reduced	*Normal*	*Delta*	*Theta*	*Absent*	*Present*	
Patients with consciousness improvement	3 (18.75%)	13 (81.25%)	3 (18.75)	13 (81.25%)	11 (68.75)	5 (31.25%)	**16**
Patients without consciousness improvement	9 (75%)	3 (25%)	7 (58.3%)	5 (41.7%)	12 (100%)	0 (0%)	**12**
All patients	12 (42.9%)	16 (57.1%)	10 (35.7%)	18 (64.3%)	23 (82.1%)	5 (17.9%)	**28**
Fisher's exact test		**p < 0.01**		**p = 0.04**		**p < 0.01**	

B	EEG after 6 months						
	Amplitude		*Frequency*		*Reactivity*		**Total**
	Unchanged	*Improved*	*Unchanged*	*Improved*	*Unchanged*	*Improved*	
Patients with consciousness improvement	14 (87.5%)	2 (12.5%)	7 (43.75%)	9 (56.25%)	7 (43.75%)	9 (56.25%)	**16**
Patients without consciousness improvement	10 (83.3%)	2 (16.7%)	11 (91.7%)	1 (8.3%)	12 (100%)	0 (0%)	**12**
All patients	24 (85.7%)	4 (14.3%)	18 (64.3%)	10 (35.7%)	19 (67.9%)	9 (32.1)	**28**
Fisher's exact test		**p = 0.6**		**p = 0.01**		**p < 0.01**	

Cells report the number of patients for each condition and p values. Percentage values (in parentheses; should be read in the horizontal direction) refer to the total reported in the last column. Improved amplitude denotes a change from reduced (< 20 µV) to normal (> 20 µV) EEG amplitude. Improved frequency denotes a change from theta to alpha band or from delta to theta band. Improved reactivity denotes reappearance of EEG reactivity.

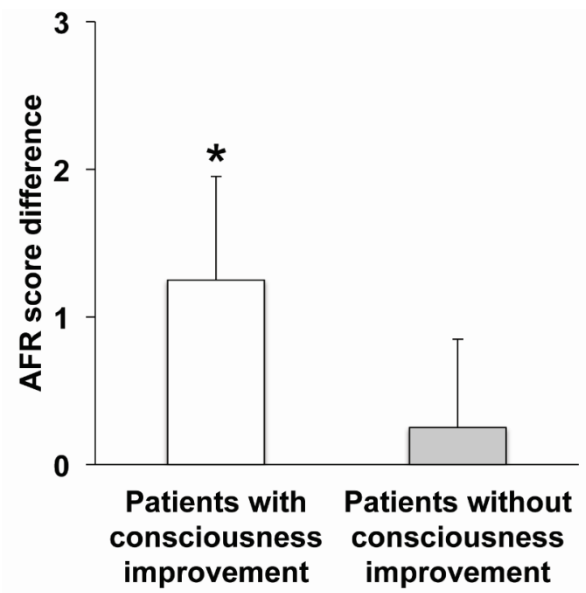

Figure 1. Amplitude-frequency-reactivity (AFR) score differences in patients with and without consciousness improvement. AFR score difference denotes the difference between the AFR score after 6 months and the same score at admission. Data are expressed as the mean and standard deviation. * $p < 0.01$.

CRS-R score changes in patients with or without EEG improvements.

After 6 months, CRS-R scores (Figure 2A) and CRS-R score improvements (Figure 2B) were higher in patients with compared to patients without AFR score changes (U=25 and 17.5; p<0.01). Among patients with an increase in AFR score, no differences were found between patients with a 1- or 2-point increase in terms of CRS-R score (U=25; p=0.5) or CRS-R score change (U=27.5; p=0.7) after 6 months. Patients who improved to E-MCS had higher AFR scores (U=10; p=0.02) (Table 2) than those who improved to MCS, but did not have higher AFR score changes from admission (U=27; p=0.6).

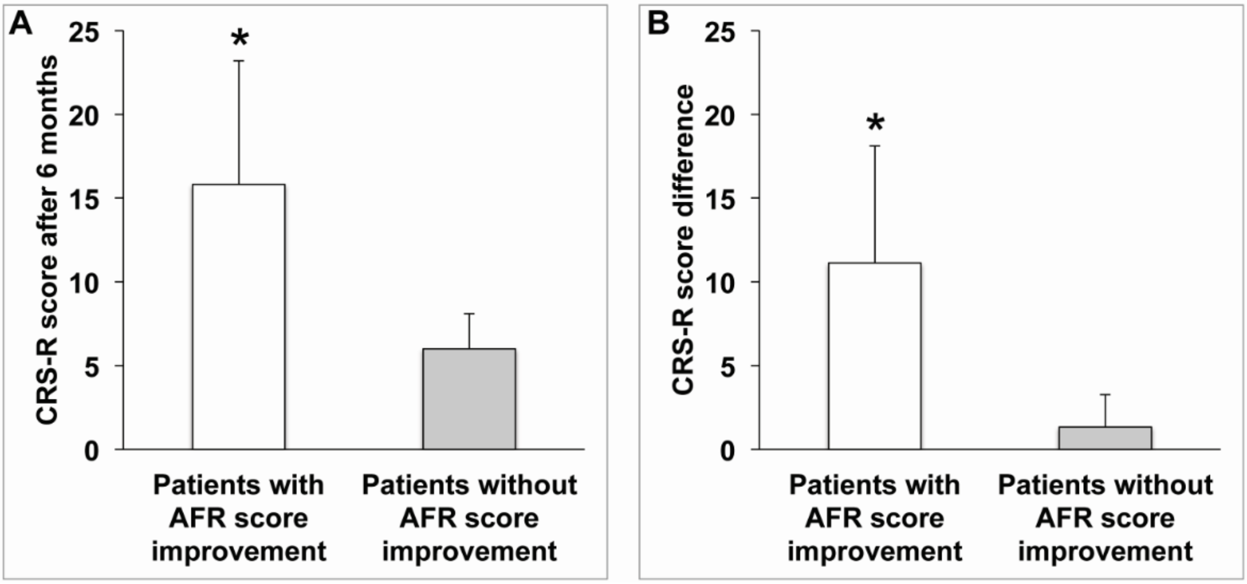

Figure 2. Coma Recovery Scale-Revised (CRS-R) scores and CRS-R score differences in patients with and without amplitude-frequency-reactivity (AFR) score improvement. CRS-R score difference denotes the difference between the CRS-R score after 6 months and the same score at admission. The AFR score improvement denotes an increase of the AFR score respect to the score at admission. Data are expressed as the mean and standard deviation. * $p < 0.01$.

Discussion

In this study, we found that changes in basic EEG characteristics may be found in most patients who emerge from UWS. In particular, the AFR score was increased in 87.5% of patients with consciousness improvement 6 months after rehabilitation admission. This percentage corresponds to 12.5% of patients with improvement in EEG background amplitude, 56.3% with improvement in dominant frequency, and 56.3% with reappearance of EEG reactivity. Conversely, the AFR score increased in only 16.7% of patients without consciousness improvement. The CRS-R score increase was about 8 times higher among patients with EEG improvements (i.e., AFR score increase) compared to those without EEG changes after 6 months. Taken together, these data show that, if the EEG improves, then patients are very likely to have improved level of consciousness as well. Moreover, this study, which had a better study design (i.e., prospective vs. retrospective design), longer follow-up (i.e., 6 vs. 3

months), and more homogeneous population (i.e., patients with UWS only, instead of patients with either UWS or MCS), confirmed previous results[4-6,9] indicating the prognostic value of standard EEG performed at rehabilitation admission in patients with UWS.

EEG changes reflect a remodeling of the electrical brain activity organization due to plastic adaptations that attempt to restore brain connections and functions after a severe brain injury.[11] Surprisingly, the background EEG amplitude was the only parameter that did not significantly change in patients who recovered consciousness. This apparently incongruous finding was due to the low rate of the low voltage pattern in the baseline EEGs of patients who improved their level of consciousness. Indeed, a baseline EEG amplitude below 20 μV was reported in only three of the 16 patients with consciousness improvement (18.8%). Two of these patients showed improvement to a normal amplitude after 6 months. These results indicate that the low voltage pattern is uncommon in patients with UWS who have good outcomes and that, if present, it tends to normalize when patients recover consciousness. On the other hand, most patients who did not recover consciousness showed reduced EEG amplitude (9/12 patients, 75%), and only two of them improved to normal amplitude after 6 months. Our data showed that the low voltage pattern is not an irreversible condition in patients with UWS, because it normalized in 33.3% of patients after 6 months. The clinical significance of this change is questionable, as it was present in patients with or without consciousness improvement. This topic warrants further consideration in a larger number of patients with reduced EEG amplitude.

Neuronal functions are temporally organized through multiple oscillations that reflect different brain functions in physiological and pathological conditions.[15] In patients with disorders of consciousness, EEG oscillations are related to the level of consciousness and outcome.[16-18] Interestingly, none of the patients with UWS had a dominant alpha band frequency at admission, and the transition from the theta to alpha dominant band was the most common frequency change in patients who recovered consciousness. This finding has clear clinical implications, because it indicates that a covert awareness should be suspected in all patients who, supposedly having UWS, show a dominant alpha frequency. The transition from delta to theta dominant frequency had an uncertain significance in this study, as it occurred in only three patients (two with and one without consciousness improvement). Theta band oscillations are typically associated with working memory,[19] memory encoding and retrieval,[20-22] and emotional regulation.[23,24] The change from the delta to theta dominant band might reflect a reorganization of the brain toward a state favorable to some cognitive and affective processes. This hypothesis is supported by the observation that most patients with good outcome had a dominant theta frequency in their baseline EEGs. On the other hand, seven of the 12 patients without consciousness improvement had a dominant delta band in their baseline EEGs, and six of them also showed a dominant delta band in the follow-up. This result indicates that the dominant delta frequency tends to persist in patients without consciousness improvement.

EEG reactivity reflects changes in overall cortical neuronal synchronization, typically in response to sensory stimuli or cognitive tasks.[25] The preserved ability to desynchronize and then resynchronize large neuronal networks in response to different stimuli is a reliable predictor of outcome in comatose and UWS patients.[6,9,26,27] At the baseline evaluation, EEG reactivity was absent in 68.8% of patients with subsequent consciousness recovery and in all patients without consciousness recovery. EEGs performed after 6 months revealed a substantial difference between the two groups: 81.9% patients without EEG reactivity at admission and with consciousness recovery showed reappearance of reactivity after 6 months, whereas no patients without consciousness recovery had a reappearance of reactivity.

Data on AFR score further strengthened the close relationship between EEG changes and clinical improvements in patients with UWS. As expected, the AFR score increased after 6 months in almost all patients with good outcomes (14/16 patients). CRS-R scores after 6 months were significantly higher in patients with AFR score changes compared to patients without AFR score changes.

Two patients with consciousness improvement did not have EEG changes (patients 4 and 8). We hypothesize that simple visual analyses were not adequate to detect EEG changes related to consciousness improvement in these patients. Similar cases should be evaluated with advanced quantitative analyses.[16,28,29] Additionally, two patients did not improve consciousness despite having AFR score changes. Taken together, these results indicate that clinical or EEG changes may occur without corresponding changes in EEG or clinical behaviors in a minority of patients.

Study limitations

A critical aspect of this study is the timing of clinical and EEG evaluations. Baseline evaluations were not performed in the acute setting (with reference to the date of the brain injury), but rather were done after patients had stabilized clinically and were being admitted to a rehabilitation department. Thus, patients were not homogeneous in terms of time since brain injury, which may have affected baseline EEG findings and subsequent EEG and clinical changes. Moreover, different etiologies may have affected the results because the number of hypoxic brain injuries was lower among patients with compared to patients without consciousness improvement.

Conclusions

EEG changes in patients with UWS may aid in the timely recognition of patients transitioning into a MCS, because there are only a few behavioral signs denoting this transition.[30] If repeated during the rehabilitative treatment, standard EEG may add valuable information about possible changes in the level of consciousness in patients with UWS. The results of this study may help clinicians to identify patients who require more accurate clinical evaluations to define their level of consciousness precisely, or to recognize those patients who need to be evaluated with advanced EEG or functional neuroimaging studies.[17,18,29,31-32] Future research should evaluate whether EEG changes parallel long-term outcomes in patients with UWS, as well as whether these changes may help clinicians in delineating prognoses in patients in a MCS.

References

1. Sitt JD, King JR, El Karoui I, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain 2014;137:2258-70.
2. Royal College of Physicians. Prolonged disorders of consciousness: National clinical guidelines. London, R.C.P., 2013.
3. Laureys S, Celesia GG, Cohadon F, et al. (2010). Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 2010;8:68.
4. Bagnato S, Boccagni C, Prestandrea C, Sant'Angelo A, Castiglione A, Galardi G. Prognostic value of standard EEG in traumatic and non-traumatic disorders of consciousness following coma. Clin Neurophysiol 2010;121:274-280.
5. Boccagni C, Bagnato S, Sant'Angelo A, Prestandrea C, Galardi G. Usefulness of standard EEG in predicting the outcome of patients with disorders of consciousness after anoxic coma. J Clin Neurophysiol 2011;28:489-492.
6. Logi F, Pasqualetti P, Tomaiuolo F. Predict recovery of consciousness in post-acute severe brain injury: the role of EEG reactivity. Brain Inj 2011;25:972-979.
7. Lechinger J, Bothe K, Pichler G, et al. CRS-R score in disorders of consciousness is strongly related to spectral EEG at rest. J Neurol 2013;260:2348-2356.
8. Estraneo A, Moretta P, Loreto V, et al. Predictors of recovery of responsiveness in prolonged anoxic vegetative state. Neurology 2013;80:464-470.
9. Bagnato S, Boccagni C, Sant'Angelo A, Prestandrea C, Mazzilli R, Galardi G. EEG predictors of outcome in patients with disorders of consciousness admitted for intensive rehabilitation. Clin Neurophysiol 2015;126:959-966.
10. Bagnato S, Boccagni C, Sant'Angelo A, Prestandrea C, Virgilio V, Galardi G. EEG epileptiform abnormalities at admission to a rehabilitation department predict the risk of seizures in disorders of consciousness following a coma. Epilepsy Behav 2016;56:83-87.
11. Bagnato S, Boccagni C, Sant'angelo A, Fingelkurts AA, Fingelkurts AA, Galardi G. Emerging from an unresponsive wakefulness syndrome: brain plasticity has to cross a threshold level. Neurosci Biobehav Rev 2013;37:2721-2736.
12. Fingelkurts AA, Fingelkurts AA, Bagnato S, Boccagni C, Galardi G. Do we need a theory-based assessment of consciousness in the field of disorders of consciousness? Front Hum Neurosci 2014;8:402.
13. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85:2020-2029.
14. Seel RT, Sherer M, Whyte J, et al. Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. Arch Phys Med Rehabil 2010;91:1795-1813.
15. Fingelkurts AA, Fingelkurts AA. EEG oscillatory states: universality, uniqueness and specificity across healthy-normal, altered and pathological brain conditions. PLoS One 2014;9:e87507.
16. Fingelkurts AA, Fingelkurts AA, Bagnato S, Boccagni C, Galardi G. EEG oscillatory states as neuro-phenomenology of consciousness as revealed from patients in vegetative and minimally conscious states. Conscious Cogn 2012;21:149-169.
17. Fingelkurts AA, Fingelkurts AA, Bagnato S, Boccagni C, Galardi G. The value of spontaneous EEG oscillations in distinguishing patients in vegetative and minimally conscious states. Suppl Clin Neurophysiol 2013;62:81-99.

18. Fingelkurts AA, Fingelkurts AA, Bagnato S, Boccagni C, Galardi G. Life or death: prognostic value of a resting EEG with regards to survival in patients in vegetative and minimally conscious states. PLoS One 2011;6:e25967.
19. Scheeringa R, Petersson KM, Oostenveld R, Norris DG, Hagoort P, Bastiaansen MC. Trial-by-trial coupling between EEG and BOLD identifies networks related to alpha and theta EEG power increases during working memory maintenance. Neuroimage 2009;44:1224-1238.
20. Fell J, Ludowig E, Staresina BP, et al. Medial temporal theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial EEG. J Neurosci 2011;31:5392-5397.
21. Rutishauser U, Ross IB, Mamelak AN, Schuman EM. Human memory strength is predicted by theta-frequency phase-locking of single neurons. Nature 2010;464:903-907.
22. Hsieh LT, Ranganath C. Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval. Neuroimage 2014;85:721-729.
23. Aftanas LI, Pavlov SV, Reva NV, Varlamov AA. Trait anxiety impact on the EEG theta band power changes during appraisal of threatening and pleasant visual stimuli. Int J Psychophysiol 2003;50:205-212.
24. Sachs G, Anderer P, Dantendorfer K, Saletu B. EEG mapping in patients with social phobia. Psychiatry Res 2004;131:237-247.
25. Bazanova OM, Vernon D. Interpreting EEG alpha activity. Neurosci Biobehav Rev 2014;44:94-110.
26. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol 2010;67:301-307.
27. Azabou E, Fischer C, Mauguiere F, et al. Prospective cohort study evaluating the prognostic value of simple EEG parameters in postanoxic coma. Clin EEG Neurosci 2016;47:75-82.
28. Fingelkurts AA, Fingelkurts AA. Operational architectonics methodology for EEG analysis: Theory and results. Neuromethods 2015;91:1-59.
29. Fingelkurts AA, Fingelkurts AA, Bagnato S, Boccagni C, Galardi G. Toward operational architectonics of consciousness: basic evidence from patients with severe cerebral injuries. Cogn Process 2012;13:111-131.
30. Bagnato S, Boccagni C, Sant'Angelo A, Fingelkurts AA, Fingelkurts AA, Galardi G. Longitudinal assessment of clinical signs of recovery in patients with unresponsive wakefulness syndrome after traumatic or nontraumatic brain injury. J Neurotrauma, in press; doi: 10.1089/neu.2016.4418.
31. Cruse D, Chennu S, Fernández-Espejo D, Payne WL, Young GB, Owen AM. Detecting awareness in the vegetative state: electroencephalographic evidence for attempted movements to command. PLoS One 2012;7:e49933.
32. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. Science 2006;313:1402.
33. Monti MM, Vanhaudenhuyse A, Coleman MR, et al. Willful modulation of brain activity in disorders of consciousness. N Engl J Med 2010;362:579-589.