Below is the unedited draft of the article that has been accepted for publication
(© Journal of Neurotrauma, 2017, Volume 34, Issue 2, P. 535-539.)

Longitudinal Assessment of Clinical Signs of Recovery in Patients with Unresponsive Wakefulness Syndrome After Traumatic or Nontraumatic Brain Injury

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ABSTRACT

Although clinical examination is the gold standard for differential diagnosis between unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS), clinical signs denoting the first occurrence of conscious behavior in patients with UWS have not been clarified. In this prospective single-center cohort study, 31 consecutive patients with UWS after traumatic brain injury (TBI, 17 patients) or non-TBI were assessed with the Coma Recovery Scale Revised (CRS-R) at admission to a rehabilitation department and after 1, 2, 3, 6, and 12 months. Of the 21 patients who recovered consciousness during the study, 90.5% recovered consciousness within the first 3 months. At the first diagnosis of emergence from UWS, 52.4% of patients showed signs of awareness in only one CRS-R subscale. In particular, 42.9% of patients showed conscious behaviors on the visual CRS-R subscale (23.8% showed visual fixation and 19.1% showed visual pursuit), and 9.5% on the motor CRS-R subscale (half showed localization to a noxious stimulus and half showed object manipulation). Moreover, 23.8% of patients showed conscious behaviors on two CRS subscales, always involving the visual and motor CRS-R subscales. Remaining patients showed conscious behaviors on more than two CRS-R subscales. In conclusion, visual fixation and visual pursuit are the commonest early clinical signs denoting MCS. When emerging from UWS, patients with TBI often showed more signs of consciousness and had higher CRS-R scores than patients with non-TBI.

Key words:
vegetative state; minimally conscious state; disorders of consciousness; traumatic brain injury; Coma Recovery Scale Revised.

INTRODUCTION

Unresponsive wakefulness syndrome (UWS, previously known as the vegetative state)[1-3] is a disorder of consciousness that follows a severe brain injury. Patients with UWS seem to be awake, but they lack any signs of awareness of self or the external world. The first stage of recovery from UWS is the minimally conscious state (MCS), a clinical condition in which minimal signs of awareness reappear.[4] Traumatic brain injury (TBI), cerebrovascular disease, and cerebral hypoxia are the commonest causes of UWS. At present, no criteria are available to predict if or when recovery from UWS will occur. Recovery depends on the ability of the brain to recover neural circuits and functions involved in conscious behaviors.[5] However, the likelihood that a patient will recover consciousness progressively decreases over time. The transition into an MCS generally occurs within 12 months in patients with TBI or 3 months in patients with non-TBI.[2]

A careful clinical examination, combined with the use of standardized assessment tools, is the gold standard for differential diagnosis between UWS and MCS. Indeed, recognizing the first signs of transition into an MCS is a challenging task, and the use of standardized tools is strongly recommended. The Coma Recovery Scale Revised (CRS-R) is considered the best scale for assessing these severe disorders of consciousness.[6,7] The CRS-R is able to differentiate UWS, MCS, and emergence from MCS (E-MCS).[6] This scale consists of 29 hierarchically organized items grouped into six subscales addressing auditory, visual, motor, oromotor/verbal, communication, and arousal functions.[6] All CRS-R subscales allow differentiation of unconscious from conscious behaviors. The first five subscales contain specific criteria to differentiate UWS and MCS, whereas the motor function and communication subscales define criteria for E-MCS.

Until now, no study has delineated the first clinical signs of transition into MCS in UWS patients. In this prospective study, we used the CRS-R to evaluate the first clinical signs denoting emergence from UWS. According to the time course of recovery from UWS, we followed up patients until 1 year after admission to a rehabilitation department, with monthly evaluations during the first 3 months after admission. The results of this study will be useful for recognizing patients in an MCS earlier, enabling specific rehabilitative treatments.

METHODS

This prospective study was conducted on 31 consecutive patients with UWS (20 males and 11 females; mean age: 42.8 ± 15.4 years) who were admitted to our Unit for Severe Acquired Brain Injury for intensive rehabilitation after an acute brain injury (mean time from brain injury to admission: 54 ± 35 days). Seventeen patients with a TBI and 14 patients with a non-TBI were recruited. Only patients with age between 18 and 70 years were included. Patients with a previous history of TBI, stroke, cerebral hypoxia, neurodegenerative disease, or infection of the central nervous system were excluded. Clinical details are reported in Table 1.

Table 1. Patient demographic and clinical details.

Patient	Gender	Age (y)	Time from brain injury to rehabilitation admission (d)	Etiology	CT/MRI data	CRS-R score at admission (subscores in parentheses)
1	M	65	63	TBI	Left frontal ischemia.	4 (Au0, V0, M2, O0, C0, Ar2)
2	M	33	53	TBI	Left fronto-parietal SaH, EH with brainstem compression.	7 (Au2, V1, M1, O1, C0, Ar2)
3	F	38	39	TBI	Right hemispheric SdH, left temporal CC, DAI.	2 (Au0, V0, M0, O0, C0, Ar2)
4	M	19	101	TBI	Right fronto-parietal SdH.	7 (Au1, V1, M2, O1, C0, Ar2)
5	F	56	54	Cerebral hypoxia	Cerebral edema.	5 (Au1, V1, M1, O0, C0, Ar2)
6	F	43	63	Cerebral hypoxia	Cerebral edema.	5 (Au1, V0, M2, O0, C0, Ar2)
7	M	45	53	TBI	Bilateral SaH, multiple CC.	4 (Au0, V0, M2, O0, C0, Ar2)
8	M	50	60	Cerebral hypoxia	Cerebral edema.	4 (Au 0, V0, M1, O1, C0, Ar2)
9	M	21	24	TBI	Cerebral edema, DAI.	5 (Au1, V0, M2, O0, C0, Ar2)
10	F	37	17	Cerebral hypoxia	Hypoxic damage in basal ganglia and corpus callosum.	5 (Au0, V1, M2, O0, C0, Ar2)
11	M	33	32	TBI	Bilateral SdH.	0 (Au0, M0, O0, C0)*
12	M	40	42	TBI	Right hemispheric SdH.	4 (Au0, V0, M1, O1, C0, Ar2)
13	M	25	26	TBI	Left fronto-temporal SdH, brain edema.	6 (Au1, V1, M1, O1, C0, Ar2)
14	M	46	26	ACA aneurysm rupture	SaH, cerebral edema.	4 (Au1, V0, M1, O1, C0, Ar4)
15	M	50	176	Encephalitis	Multiple areas of cortical and subcortical damage.	6 (Au1, V1, M2, O0, C0, Ar2)
16	F	46	85	Neurosurgery for meningioma	Cerebral edema and multiple ischemic lesions.	6 (Au1, V1, M2, O0, C0, Ar2)
17	M	23	24	TBI	Left temporo-occipital and bilateral frontal SaH.	4 (Au0, V0, M2, O0, C0, Ar2)
18	F	63	23	Cavernous malformation rupture	SaH with hydrocephalus	3 (Au0, V0, M2, O0, C0, A2)
19	M	65	31	TBI	Right hemispheric EH.	6 (Au1, V0, M2, O1, C0, Ar2)
20	F	30	29	Cerebral hypoxia	Signs of cortical and subcortical hypoxic damage.	5 (Au1, V0, M2, O1, C0, Ar2)
21	F	70	39	TBI	Left temporo-parietal SdH, left temporal CC.	4 (Au0, V0, M1, O1, C0, Ar2)
22	F	24	89	TBI	DAI.	6 (Au1, V0, M2, O1, C0, Ar2)
23	M	60	17	Cerebral hypoxia	Signs of subcortical hypoxic damage.	3 (Au0, V0, M1, O0, C0, Ar2)
24	F	55	58	Cerebral hypoxia	Signs of cortical and subcortical hypoxic damage.	5 (Au0, V0, M2, O1, C0, Ar2)
25	F	56	77	MCA aneurysm rupture	SaH with hydrocephalus.	5 (Au0, V0, M2, O1, C0, Ar2)
26	M	56	86	Cerebral hypoxia	Cerebral edema.	5 (Au0, V0, M2, O1, C0, Ar2)
27	M	38	27	TBI	DAI.	6 (Au1, V1, M1, O1, C0, Ar2)
28	M	56	91	ACA aneurysm rupture	SaH with hydrocephalus.	3 (Au0, V0, M0, O1, C0, Ar2)
29	M	19	30	TBI	Left temporo-parietal CC with SdH, midbrain contusion.	7 (Au1, V1, M2, O1, C0, Ar2)
30	M	22	35	TBI	Cerebral edema and DAI.	5 (Au0, V0, M2, O1, C0, Ar2)
31	M	54	112	TBI	Multiple areas of cortical damage.	6 (Au1, V1, M1, O1, C0, Ar2)

*Patient no. 11 had a bilateral deficit of the oculomotor nerve associated with posttraumatic blindness, which prohibited evaluation of the visual and arousal CRS-R subscales. Etiology and CT/MRI data abbreviations: ACA, anterior communicating artery; CC, cortical contusion; DAI, diffuse axonal injury; EH, epidural hematoma; MCA, middle cerebral artery; SaH, subarachnoid hemorrhage; SdH, subdural hematoma; TBI, traumatic brain injury. CRS-R subscale abbreviations: Au, auditory; V, visual; M, motor; O, oro-motor / verbal; C, communication; Ar, arousal.

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 the CRS-R, which provides standardized criteria for the diagnosis of UWS, MCS, and E-MCS.[6] Diagnosis of UWS was accepted if confirmed at all three evaluation times, to reduce the risk of misdiagnosis due to fluctuations in patients' level of consciousness. To identify clinical signs of recovery from UWS, the same assessment was repeated after 1, 2, 3, 6, and 12 months, until the first occurrence of signs denoting a transition into MCS. Clinical assessments were not performed if patients had medical complications that may impact their alertness (e.g., fever). No changes in the usually administered drugs were made. Clinical signs of recovery from UWS were reported according to the CRS-R subscales. Differences in patient demographic and clinical data were assessed by Student's *t*-test.

The ethics committee of Fondazione Istituto San Raffaele G. Giglio (Cefalù, Italy) approved this study. Patients' legal guardians gave their written informed consent to all procedures.

RESULTS

No differences were found between patients with TBI and non-TBI in terms of days between brain injury and admission (p = 0.3) or CRS-R scores at admission (p = 0.6). Patients with TBI were younger than patients with non-TBI (37.3 ± 17.3 and 50.3 ± 9.1 years, respectively; p = 0.01).

Twenty-one patients recovered consciousness during the study, accounting for 76.5% of patients with TBI and 57.1% of patients with non-TBI. Seven patients were classified as UWS 12 months after admission. Two patients (nos. 21 and 26) died during the study without recovering consciousness (before the 6- and 2-month evaluation, respectively). One patient (no. 20) was transferred to another hospital before the 12-month evaluation without recovery of consciousness.

Twelve patients recovered consciousness within the first month after admission. Of these 12 patients, 11 patients were diagnosed as MCS and one patient as E-MCS. Five patients evolved into MCS by the 2-month evaluation. Two patients evolved into MCS by the 3-month evaluation. Two other patients progressed into MCS after 6 months. No further recovery of consciousness occurred by 12 months after admission.

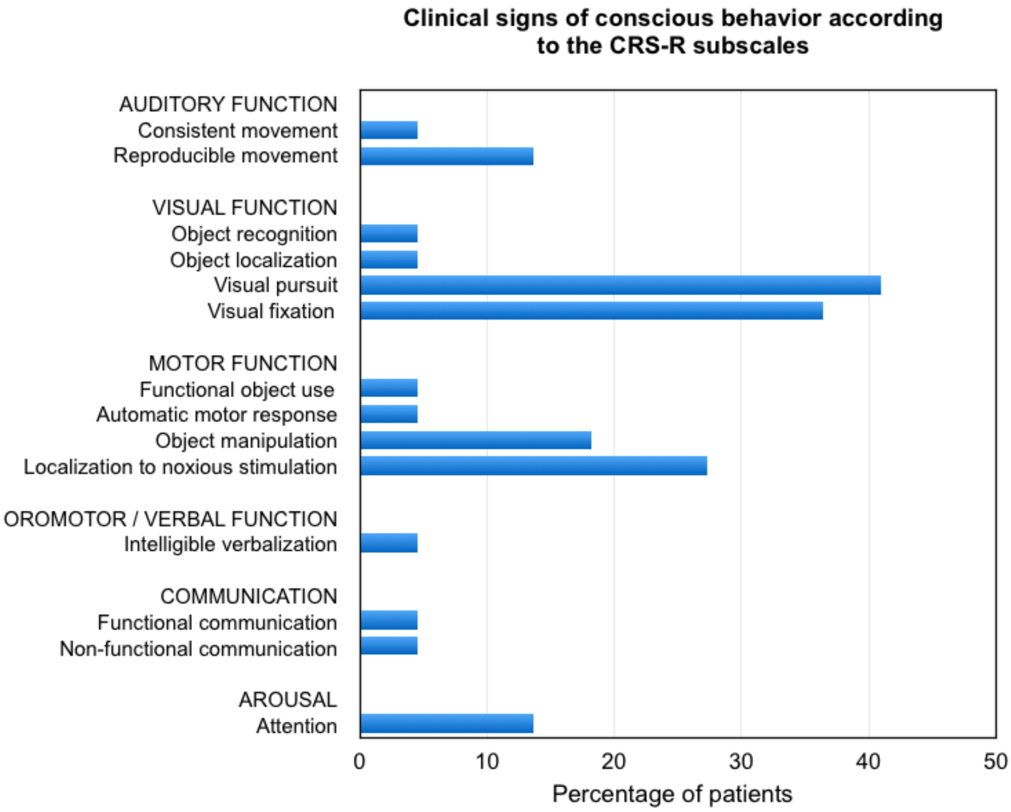
Among the 21 patients who recovered consciousness during the current study, 11 patients (38.5% of patients with a TBI etiology and 75% with a non-TBI etiology) showed only one sign of conscious behavior at the first diagnosis of emergence from UWS (Table 2). Nine patients showed a sign of awareness on the CRS-R visual function subscale: five patients showed visual fixation, and four patients showed visual pursuit (Table 2). Two other patients showed their first sign of recovery on the CRS-R motor function subscale: one patient presented localization to a noxious stimulus, and one patient showed object manipulation (Table 2).

Table 2. First signs of consciousness in patients emerging from an UWS.

Patient	Evaluation in which signs of consciousness appeared (days from brain injury in parentheses)	CRS-R score (subscores in parentheses)	Signs denoting consciousness according to the CRS-R
Patients with TBI			
1	1 month (93)	23 (Au4, V5, M6, O3, C2, Ar3)	Functional object use, functional communication.
2	2 months (113)	7 (Au1, V2, M2, O0, C0, Ar2)	Visual fixation.
3	6 months (219)	16 (Au3, V4, M5, O1, C0, Ar3)	Reproducible movement to command, object localization, automatic motor response, attention.
4	1 month (131)	9 (Au2, V2, M2, O1, C0, Ar2)	Visual fixation.
9	2 months (84)	10 (Au2, V3, M3, O0, C0, Ar2)	Visual pursuit, localization to noxious stimulation.
11	1 month (62)	10 (Au3, M4, O2, C1)	Reproducible movement to command, object manipulation, nonfunctional communication.
13	1 month (56)	13 (Au2, V3, M4, O1, C0, Ar3)	Visual pursuit, object manipulation, attention.
17	1 month (54)	12 (Au2, V3, M2, O2, C0, Ar2)	Visual pursuit.
19	1 month (61)	14 (Au3, V3, M4, O2, C0, Ar2)	Reproducible movement to command, visual pursuit, object manipulation.
27	1 month (57)	12 (Au2, V3, M3, O2, C0, Ar2)	Visual pursuit, localization to noxious stimulation.
29	1 month (60)	9 (Au1, V2, M3, O1, C0, Ar2)	Visual fixation, localization to noxious stimulation.
30	1 month (65)	8 (Au1, V1, M3, O1, C0, Ar2)	Localization to noxious stimulation.
31	1 month (142)	9 (Au2, V3, M1, O1, C0, Ar2)	Visual pursuit.
Patients with non-TBI			
5	3 months (144)	10 (Au2, V2, M3, O1, C0, Ar2)	Visual fixation, localization to noxious stimulation.
8	2 months (120)	9 (Au2, V2, M2, O1, C0, Ar2)	Visual fixation.
10	2 months (77)	6 (Au1, V2, M1, O0, C0, Ar2)	Visual fixation.
14	6 months (206)	10 (Au2, V3, M2, O1, C0, Ar2)	Visual pursuit.
16	1 month (115)	8 (Au1, V2, M2, O1, C0, Ar2)	Visual fixation.
18	3 months (113)	6 (Au0, V0, M4, O1, C0, Ar1)	Object manipulation.
25	2 months (137)	12 (Au2, V3, M3, O2, C0, Ar2)	Visual pursuit, localization to noxious stimulation.
28	1 month (121)	9 (Au1, V3, M2, O1, C0, Ar2)	Visual pursuit.

For each CRS-R subscale, the clinical sign of consciousness with the highest CRS-R score is reported. Patient identifier nos. and CRS-R subscale abbreviations refer to data reported in Table 1. Patient no. 1 was classified as E-MCS 1 month after admission. Only signs denoting E-MCS were reported thereafter.

Five patients showed signs of awareness in two different CRS-R subscales. Notably, all five of these patients showed signs of consciousness in the visual and motor CRS-R subscales. The remaining five patients showed signs of awareness in more than two subscales (Table 2). Supplemental Figure 1 reports the occurrence of signs of recovery on the CRS-R subscale items.



Supplemental figure 1 legend. The CRS-R has a hierarchically organized structure. For each subscale, only the conscious behavior with the highest score is reported.

At the first diagnosis of emergence from UWS, patients with TBI showed signs of conscious behavior in more CRS-R subscales than patients with non-TBI (2.3 ± 1.5 vs. 1.3 ± 0.5, respectively; p = 0.03). Moreover, patients with TBI had a trend toward higher CRS-R scores than patients with non-TBI (11.7 ± 4.3 vs. 8.8 ± 2.1, respectively; p = 0.05). Finally, patients with TBI showed a trend toward earlier first occurrence of conscious behavior compared to patients with non-TBI (92.1 ± 48.5 days from brain injury vs. 129.1 ± 36.9 days, respectively; p = 0.06) (Table 2).

DISCUSSION

In this study, we found that more than half of patients who emerge from UWS show only one sign of conscious behavior, and that the commonest signs of emergence from UWS involve the visual system. In particular, visual fixation and visual pursuit were the only clinical signs of consciousness in 42.9% of patients at their first diagnosis of MCS. This percentage increased to 85.7% if signs of awareness on the CRS-R visual subscale occurred in combination with signs from other CRS-R subscales. Moreover, with the current timing among consecutive assessments, our results suggest that patients with TBI often emerge from UWS with more clinical signs of conscious behavior compared to patients with non-TBI.

Vision is the main sense through which we explore the external world, and the visual modality dominates in multisensory integration.[8] Signs such as the ability to open the eyes and to move them in response to stimuli are related to the levels of arousal and awareness. Therefore, it is not surprising that visual fixation and visual pursuit are the commonest first recognizable signs of awareness during emergence from UWS. This finding agrees with evidence that behavioral signs of consciousness may be detected on the visual CRS-R subscale in most MCS patients.[9]

Localization of a noxious stimulus and object manipulation were the earliest clinical signs of awareness in 9.5% of patients. This result suggests that motor behaviors should be carefully assessed in patients who do not show visual signs of consciousness recovery. The prominent role of the visual and motor subscales in detecting conscious behaviors was further confirmed by the finding that these two subscales were always implicated in the 23.8% of patients who showed signs of awareness on two CRS-R subscales.

One patient (no. 11) had a visual impairment that prevented him from showing conscious behaviors on the visual CRS-R subscale; however, he showed conscious behaviors on the other three CRS-R subscales. These data suggest that the CRS-R provides several tools to reveal conscious behaviors, even in patients with visual impairment.

Our results showed that 90.5% of patients recovered consciousness within 6 months after brain injury. Patients with TBI showed a trend toward an earlier occurrence of conscious behaviors compared to patients with non-TBI, although this trend was not statistically significant. The reduced number of patients with non-TBI who recovered consciousness during the study probably conditioned this lack of significance. These data, which were obtained by using a prospective study design and a standardized clinical tool, confirm previous results[2] showing that patients have the best chances of recovering consciousness within the first months after brain injury. Patients with a TBI etiology often showed more than one sign of conscious behavior. Although this finding is consistent with evidence that UWS due to TBI has a better outcome than UWS due to non-TBI,[2] we caution that the result should be confirmed in a larger population of patients. Indeed, patients with UWS and TBI were younger than those with non-TBI, and their different behaviors might be related to differences in age rather than etiology.

A critical point of this study is the timing of clinical evaluations. Ideally, the best time for the first assessment of patients should be at the transition from a coma into UWS. Unfortunately, these data were not available because patients were not evaluated with standardized tools in the acute setting. Moreover, according to the expected time course of recovery from UWS, we arbitrarily chose to perform monthly evaluations in the first 3 months, and, subsequently, after 3 and 6 months. This study design enabled us to detect single behavioral signs of recovery in more than half of patients who recovered consciousness, achieving 75% in non-TBI cases. However, patients with TBI often showed more than one sign of conscious behavior. This result may be due to the emergence from UWS with more than one clinical sign of conscious behavior, or it may be ascribed to an overly wide time window between clinical evaluations. Future studies should be designed to provide shorter time intervals between clinical evaluations in patients with TBI.

Advanced electroencephalographic and functional neuroimaging techniques may help in distinguishing minimally conscious patients from those who are still unconscious.[10,11] Unfortunately, these techniques are not conventional and require highly specialized expertise. For this reason, in most patients, the clinical examination is the only way to assess the level of consciousness. Clinicians should carefully research and be able to recognize those signs that will reveal the first occurrence of conscious behavior in patients with UWS.

Author Disclosure Statement

No competing financial interests exist.

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