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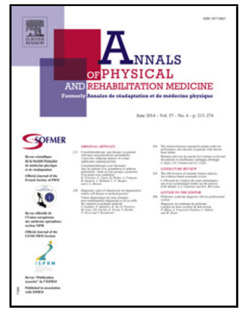

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Which behaviors are first to emerge during recovery of consciousness after severe brain injury?

Abstract

Background. Early detection of consciousness after severe brain injury is critical for establishing an accurate prognosis and planning appropriate treatment.

Objectives. To determine which behavioral signs of consciousness emerge first and to estimate the time course to recovery of consciousness in patients with severe acquired brain injury.

Methods. Retrospective observational study using the Coma Recovery Scale-Revised and days to recovery of consciousness in 79 patients (51 males; 34 with traumatic brain injury; median [IQR] age 48 [26–61] years; median time since injury 26 [20–36] days) who transitioned from coma or unresponsive wakefulness syndrome (UWS)/vegetative state (VS) to the minimally conscious state (MCS) or emerged from MCS during inpatient rehabilitation.

Results. Visual pursuit was the most common initial sign of MCS (41% of patients; 95% CI [30–52]), followed by reproducible command-following (25% [16–35]) and automatic movements (24% [15–33]). Ten other behaviors emerged first in less than 16% of cases. Median [IQR] time to recovery of consciousness was 44 [33–59] days. Etiology did not significantly affect time to recovered consciousness.

Conclusion. Recovery of consciousness after severe brain injury is most often signaled by reemergence of visual pursuit, reproducible command-following and automatic movements. Clinicians should use assessment measures that are sensitive to these behaviors because early detection of consciousness is critical for accurate prognostication and treatment planning.

Keywords. brain injury, vegetative state, minimally conscious state, outcome

Introduction

Severe brain injury frequently results in a period of altered consciousness characterized by impaired arousal and awareness [1,2]. Disorders of consciousness (DoC) include coma, a state of continuous eye closure and no behavioral signs of self or environmental awareness [3]; the vegetative state (VS), also referred to as unresponsive wakefulness syndrome (UWS), in which there is eye-opening but still no behavioral signs of awareness [4]; and the minimally conscious state (MCS), a condition characterized by reproducible but fluctuating behavioral signs of awareness. Emergence from MCS (eMCS) is marked by recovery of reliable communication and/or appropriate use of objects [5]. Detecting the transition from an unconscious to conscious state is critically important in clinical management, discharge disposition planning and family counseling. Unfortunately, diagnostic error remains high in this population, consistently reported to be around 40% [6–8].

The Coma Recovery Scale-Revised (CRS-R) [9], a standardized behavioral assessment scale consisting of 23 items hierarchically organized within 6 subscales that assess auditory, visual, motor, verbal, communication and arousal functions, is recommended for clinical use in patients with DoC by the American Congress of Rehabilitation Medicine in view of its strong psychometric properties [10]. Diagnostic assessment with the CRS-R has been shown to outperform routine bedside examination [6]. Despite the increased sensitivity for detecting consciousness afforded by the CRS-R, diagnosis may be confounded by factors such as fluctuations in vigilance [11], neuromuscular dysfunction, sensory deficits or unrecognized medical complications such as subclinical seizure activity [12]. This challenge is illustrated by a recent study involving patients with chronic DoC at approximately 4 years post-injury in which the investigators found it necessary to perform 5 CRS-R examinations over a 2-week period before the rate of diagnostic error could be reduced to 5% [13].

The term MCS was first introduced in 1997 to replace the term, "minimally responsive state," [14] to clearly differentiate individuals with at least partial preservation of conscious awareness from those lacking any sign of consciousness (i.e., coma, VS). In 2002, consensus-based diagnostic criteria for MCS were published and included the following behavioral features: command-following, intelligible verbalizations, gestural or verbal yes/no responses and non-reflexive behaviors that occurred in contingent relation to specific triggering stimuli (e.g., smiling or crying to a familiar voice, sustaining fixation on, visually tracking or reaching for an object in space) [5]. On the basis of these criteria, the CRS-R was modified and now includes 11 items designed to detect behavioral signs of MCS as well as 2 additional items to identify patients who have emerged from MCS (see Table 1).

Early detection of consciousness after severe brain injury is critical to establishing an accurate prognosis and planning appropriate treatment. Recovery of consciousness is marked by the transition from coma or UWS/VS to MCS. Identifying the first behavior marking the transition from UWS/VS to MCS may facilitate clinical decision-making regarding goals of care and recommendations concerning specific treatment interventions, including rehabilitation. Previous studies have shown that visual behaviors typically emerge first in individuals transitioning from UWS/VS to MCS. In a study of 20 individuals with DoC undergoing inpatient rehabilitation, 55% were diagnosed as being conscious based exclusively on visual behaviors captured by the CRS-R visual subscale [15]. A larger multicenter study involving patients in the intensive care setting, rehabilitation centers and long-term care facilities found that in 83% of the sample, the diagnosis of MCS was based on visual responses captured by the CRS-R [16]. In a recent study of 282 patients in chronic MCS, visual fixation and pursuit were the most frequently observed markers of consciousness to emerge (57% and 52% of cases, respectively), followed by reproducible movement to command (51%) [17]. The same study found that visual fixation, visual pursuit, reproducible movement to command, localization to pain and automatic motor behavior, alone or combined, identified 99% of patients in MCS. Finally, Bagnato and colleagues showed that among 31 individuals admitted to a rehabilitation program in UWS/VS, 20 recovered conscious awareness within 1 year, most often signaled by reemergence of visual fixation and pursuit [18].

Despite strong evidence that visual fixation and pursuit often emerge first in patients recovering from coma and UWS/VS, over-reliance on these behaviors may be problematic. Bruno and colleagues challenged the premise that visual fixation is representative of consciousness because they found no difference in cortico-cortical connectivity of the visual cortex on FDG-PET or in recovery rates between patients who demonstrated fixation and those who did not [19]. A review by Overbeek and others concluded that the existing evidence in support of visual fixation and pursuit as signs of consciousness is inconclusive because of confounding factors in assessment (e.g., orbital injury, oculomotor dysfunction), inconsistent operational definitions and other factors [20]. Apart from these concerns about the relevance of fixation and pursuit to consciousness, previous natural history studies focusing on recovery of consciousness were compromised by methodologic limitations including assessment of MCS behaviors without controlling for time since injury and failure to stratify cases with traumatic and non-traumatic brain injury (TBI, non-TBI).

To address these concerns, we aimed to monitor the frequency with which 13 different behavioral markers of consciousness first emerge in patients transitioning from coma or UWS/VS to MCS or eMCS. Our secondary aim was to determine whether the etiology of injury (TBI vs non-TBI) affected the emergence of specific behavioral markers of consciousness or the time to emergence of consciousness.

Material and methods

Procedures

Demographic and behavioral data were retrospectively extracted from a REDCap [21] database that houses clinical data elements collected by multidisciplinary rehabilitation teams caring for patients admitted to a specialized inpatient DoC rehabilitation program. During the program, the CRS-R is administered twice per week until discontinuation criteria are met (i.e., maximum score is attained on the Motor, Communication and Arousal subscales over 3 consecutive assessments, signifying eMCS). Participants met the following inclusion criteria: 1) at least 17 years old, 2) documented medical diagnosis of coma or CRS-R–based diagnosis of UWS/VS on admission to the DoC program and 3) evidence of transition to consciousness during the inpatient rehabilitation stay, defined as 2 consecutive complete CRS-R assessments obtained within 7 days indicating a new MCS or eMCS diagnosis.

Outcomes

We investigated the following outcomes: 1) incidence of the first behavioral marker(s) of consciousness to emerge after coma or UWS/VS, 2) time to recovery of consciousness and, 3) effect of etiology (TBI vs non-TBI) on the incidence of first behavioral marker(s) and time to recovery of consciousness. We also explored whether etiology had a significant influence on CRS-R total score and number of conscious behaviors recovered at the time of recovery of consciousness. We defined recovery of consciousness as emergence from coma or UWS/VS to MCS or eMCS. Table 1 shows the operational definitions of the CRS-R subscale items that represent behavioral signs of MCS and eMCS.

Statistical analyses

We used descriptive statistics (medians, interquartile ranges [IQR]) to summarize the demographic and clinical characteristics of the sample. We calculated incidence rates for the first behavioral sign of MCS or eMCS to emerge by using percentages with 95% confidence intervals (CIs). Differences between the TBI and non-TBI groups in time to recovery of consciousness, CRS-R total score at the time of transition and number of conscious behaviors recovered at the time of transition were tested by Wilcoxon (W) Rank Sum tests. Results were considered significant at $p < 0.05$. To investigate the effect of etiology on the emergence of conscious behaviors, behaviors were clustered into 3 categories: 1) language abilities (i.e., consistent and reproducible command following, intelligible verbalization, intentional and functional communication); 2) motor abilities (i.e., functional object use, automatic movement, object manipulation, localization to pain); and 3) visuoperceptual abilities (object recognition, object localization, visual pursuit, visual fixation). Differences between TBI and non-TBI groups were tested by Fisher exact test. For this analysis, multiple comparisons using

Bonferroni correction (3 comparisons) were performed and results were considered significant at $p < 0.016$ (i.e., 0.05/3).

Results

Between June 2012 and August 2017, 110 patients with severe acquired brain injury were admitted to the DoC program in an unconscious state (6 comatose; 104 with UWS/VS; 70 males; 52 with TBI; median [IQR] age 44 [27–60] years; median 28 [21–39] days after injury). Causes of non-traumatic injury included subarachnoid hemorrhage, intracerebral hemorrhage, subdural hematoma, cardiac arrest, aneurysm rupture, and hydrocephalus. As presented in Figure 1, 79 patients met the inclusion criteria (51 males; 6 comatose; 73 with UWS/VS; 34 with TBI; median age 48 [26–61] years; median 26 [20–36] days after injury).

The median [IQR] time patients were followed was 61 [42–98] days and the median number of assessments conducted per patient was 16 [11–25). The median time from program admission to baseline CRS-R exam was 1 [1–1] day and the median time between consecutive CRS-R assessments was 4 [3–5] days. The TBI group was significantly younger than the non-TBI group (median TBI age 33 [23–53] vs 57 [33–64] years, W=1077; p=0.002). The TBI and non-TBI groups did not differ in initial CRS-R total score (median 4 [3–6] vs 4 [3–6], W=748; p=0.869) or time from injury to admission (28.5 [20–36] vs 25 [20–36], W=689; p=0.454) (Table 2).

Emergence of first signs of MCS or eMCS

Visual pursuit was the most common initial behavioral sign of MCS, observed in 41% (95% CI 30–52) of individuals recovering from coma and UWS/VS (Figure 2). The next 2 most commonly observed behavioral signs of MCS, observed in approximately one quarter of participants, were reproducible movement to command (25%; 95% CI [16–35]) and automatic movement (24%; 95% CI [15–33]). The remaining 10 behavioral markers of consciousness emerged first in less than 16% of the sample.

In 72% (95% CI [62–82], n=57) of participants, recovery of consciousness was signaled by the emergence of a single behavior; in 16% (95% CI [8–24], n=13), 2 behavioral signs of MCS emerged within 7 days of recovery of consciousness; and in 6% (95% CI [0–10], n=5), 3 behaviors emerged within 7 days of transition.

Time to emergence of consciousness

The median [IQR] time to emergence of the first sign(s) of MCS or eMCS was 44 [33–59] days after injury and 14 [6–26] days after admission to the DoC program. The TBI and non-TBI groups did not differ in time to recovery of consciousness ($W=931$; $p=0.517$), number of conscious behaviors recovered at the time of transition to consciousness ($W= 673$; $p=0.250$) or total CRS-R score at the time of transition ($W = 664.5$; $p=0.317$) (Table 2).

All but 2 participants showed the typical course of recovery, progressing from coma to UWS/VS, MCS and then eMCS. Two patients transitioned directly from UWS/VS to eMCS by recovering functional object use. When behaviors were categorized into domain-specific clusters, we found some influence of etiology of injury on the frequency with which specific behaviors marked the transition to consciousness. More patients with TBI than non-TBI recovered motor signs of MCS first ($p=0.011$) (Figure 3). We found no between-group differences in language ($p=0.99$) or visual ($p=0.066$) clusters.

Discussion

Recovery of consciousness is a critical milestone in patients who sustain severe brain injury. Early detection of consciousness portends a more favorable prognosis [22,23] and is often required for admission to an inpatient rehabilitation facility. Bedside behavioral assessment, the gold standard for detecting conscious awareness, suggests that visual fixation and pursuit are often the first behavioral signs of consciousness to emerge in patients recovering from coma and UWS/VS. However, these behaviors cannot always be accurately assessed. The aim of this study was to systematically monitor behavioral recovery in patients with severe acquired brain injury to capture the first behavior(s) signaling the transition from coma or UWS/VS to eMCS. We also investigated the length of time from onset to transition to MCS, and the effect of etiology (TBI vs non-TBI) on behavioral recovery.

Among the 13 behavioral signs of MCS and eMCS monitored, visual pursuit emerged first in most patients, accounting for 41% of participants. Visual pursuit is well-documented as an early indicator of recovery of consciousness [15,24,25]. This finding likely reflects at least partial recovery of brainstem-cortical connectivity necessary for support of both basic arousal functions and eye movements. Inputs from the vestibular nuclei to the pons mediate arousal regulation and activate downstream frontal and parietal cortices responsible for eye movement control [26]. Although we did not find a significant between-group difference, both visual pursuit and fixation were observed more frequently in non-TBI than TBI participants, possibly suggesting better preservation of this pathway in individuals with anoxic and vascular injuries.

Reproducible command-following and automatic movement were the next 2 most frequent signs of MCS to emerge first, observed in approximately 25% of participants. Unlike visual fixation and pursuit, command-following is recognized as a definitive sign of conscious awareness [27] and, as such, is widely used in bedside examination. Prior studies involving patients with MCS report demonstrable evidence of command-following in 14% to 51% of cases [16–18]. Apart from the current investigation, only one other study prospectively monitored behavioral markers of recovery of consciousness [18]. Bagnato and colleagues found that reproducible command-following marked the transition from unconsciousness to consciousness in 14% of 21 patients studied, and no patient was able to follow commands consistently (defined as clearly discernible responses in 4 consecutive trials of 2 different commands). Our findings fall within the fairly broad range previously reported. It is not clear what accounts for the variability in the incidence of command-following, although this may be due to differences in how command-following is assessed or the confounding influence of sedating medications. There are no universal standards governing which commands should be administered, how many trials should be conducted or how responses should be interpreted. In line with prior studies, we found that consistent command-following rarely reemerges within 7 days of recovery of consciousness. Bagnato and colleagues also reported lower rates of automatic movement (5% vs 24% in the present sample) and higher rates of object manipulation (18% v. 5% in the present sample) [18], again, possibly reflecting differences in assessment or scoring methods.

Automatic movements are over-learned behaviors that tend to be repetitive and are triggered by interoceptive or exteroceptive stimuli. They closely resemble automatisms [28], actions that occur without intent during episodes of complex partial seizure. Examples of automatic motor behavior include nose-scratching, hand-wringing and assuming stereotypical postures. The presence of automatic behavior suggests at least partial preservation of self and environmental awareness. These behaviors are triggered when primary sensory cortices detect an internal (e.g., itch) or external (e.g., object entering the visual field) stimulus. Neural signals are then sent to downstream association cortices for further perceptual encoding (e.g., what kind of object is this?), and ultimately to the motor cortex, which initiates the specific movement sequence associated with the triggering stimulus (e.g., scratching the itch, grasping the object). These processing steps suggest that some awareness of self and environment must be retained to engage this type of behavior. This premise is supported by a study by Remi and colleagues [29]. These investigators followed a cohort of patients with severe acute stroke and found that patients who exhibited automatic behavior, specifically, leg-crossing while seated, achieved significantly more favorable functional outcomes at 1 year post-injury.

The remaining 10 behavioral signs of MCS or eMCS emerged first in 0 to 15% of our participants. This is not surprising given that 6 of these 10 behaviors — functional communication, intentional communication, functional object use, consistent command-following, intelligible verbalization and object recognition — depend on well-preserved network connectivity. It is not clear why the remaining four behaviors — object manipulation, object localization, localization to pain and visual fixation — infrequently emerged first.

In most cases (72%), recovery of consciousness was heralded by a single behavior. This finding strongly suggests that the evaluation of individuals with DoC should incorporate a range of different behaviors. Inadequate behavioral sampling likely contributes to the 40% misdiagnosis rate consistently reported in the literature [6–8]. The approach to assessment should include procedures designed to reliably detect visual pursuit, command-following and automatic movements. Visual pursuit should be assessed by using a mirror because of evidence that the auto-referential aspect of one's own face is a highly salient stimulus [30]. Eye tracking devices adapted for patients with DoC have also been developed [31] but may be difficult to calibrate due to associated cognitive, visual, visuoperceptual and oculomotor disturbance. Command-following should be systematically assessed with standardized administration and scoring procedures such as those used by the CRS-R [9], Wessex Head Injury Matrix [32] or the Sensory Modality Assessment and Rehabilitation Technique [33]. Individualized quantitative behavioral assessment procedures, which rely on single-subject research methods, can reliably differentiate command-following from random behavior [34,35]. Automatic movements, by their nature, may be difficult to elicit on bedside examination. The CRS-R includes assessment methods designed to capture all these behaviors[9]. Serial assessment remains essential in view of the fluctuations in arousal and vigilance that characterize this population. [13,34]

Regarding time to recovery of consciousness, the first behavioral sign of MCS or eMCS tended to emerge approximately 6 weeks after the injury (median 44 days). This finding generally concurs with 2 prior studies reporting recovery of consciousness within 12 weeks of injury [18,36]. Precise behavior-specific estimates of time to recovery of consciousness could not be provided by either of the earlier studies because neither performed weekly follow-up. Like Bagnato, et al. [18], we did not find a significant difference between the TBI and non-TBI groups in time to recovery of consciousness.

We found that motor behaviors marked the transition to consciousness significantly more often in patients with TBI relative to those with non-TBI, possibly reflecting pathophysiologic differences between these groups. Non-traumatic lesions arising from severe hypoxic-ischemic events preferentially damage brain regions with high oxygen consumption demands [37,38]. Involvement of the basal ganglia, which have high metabolic demand for oxygen and play an important role in motor control, may account for the lower frequency of automatic movements noted in the non-TBI group. In a few cases, behaviors reflecting higher levels of neurologic function (e.g., functional object use) emerged before lower-level behaviors (e.g., localization to pain) during the transition to consciousness. More frequent (daily vs weekly) CRS-R assessment may have captured these lower-level behaviors at the time of transition.

This study has some limitations that may affect the generalizability of the results. We included only individuals who transitioned to or emerged from MCS after admission to an inpatient rehabilitation facility at 3 to 5 weeks post-injury, which represents a selection bias. Thus, patients who transitioned earlier than 3 weeks after injury were not captured and may have experienced a different behavioral recovery profile. We are not aware of any studies that systematically tracked recovery of consciousness during the acute period by using repeated standardized neurobehavioral assessment. Acute studies are necessary to more fully characterize the natural history of recovery of consciousness. Second, this study was conducted at a single site. Although the sample size was fairly large and the demographic characteristics were typical of subacute DoC, there may be local differences that limit generalizability. Finally, the data were collected by clinical staff, which raises the possibility of procedural variability. Some behaviors, such as visual fixation and pursuit, are particularly susceptible to this problem. There is evidence that both visual fixation and pursuit are more likely to occur in response to presentation of a mirror as compared to an object or person [30,39,40]. This concern is mitigated by the fact that the CRS-R has strong inter-rater reliability [9,41,42] and all clinical staff were required to undergo training before using the scale.

We also wish to raise a more general issue that relates to the focus of the study. The relationship between observable behavior and the "contents of consciousness" is unclear because one cannot reliably infer self or environmental awareness based solely on behavior [43–45]. In the absence of subjective reports, behavior is a non-specific indicator of level of consciousness. For example, smiling may represent a cognitively-mediated conscious state (as in amusement while listening to a humorous story), the pathologic release of an over-learned behavioral response (i.e., as in pseudobulbar affect) or even reflexive activity (as in muscle spasm arising from risus sardonicus) [44]. In light of this concern, Naccache and colleagues have proposed a re-conceptualization of traditional behavioral signs of consciousness. They suggest that behavioral signs such as visual fixation and pursuit should be described as "cortically-mediated behaviors" rather than "signs of consciousness" to avoid over-interpretation in terms of subjective content [43]. In contrast, the recently released US-based practice guidelines for the diagnosis of patients with DoC published by the American Academy of Neurology, American Congress of Rehabilitation Medicine and National Institute on Disability, Independent Living and Rehabilitation Research endorsed these behaviors as "signs of consciousness," which illustrates the ongoing debate around this issue [34].

Conclusions

In patients recovering from coma and UWS/VS during inpatient rehabilitation, visual pursuit, command-following and automatic movements are typically the first behavioral signs marking the transition to MCS or eMCS (observed in 24-41% of our participants). Among patients who remain unconscious for 3 to 5 weeks after injury, recovery of consciousness is usually marked by a single behavior and the median time to recovery is approximately 44 days in both TBI and non-TBI cases. Clinicians should ensure that assessment methods are especially sensitive to these 3 behaviors. Future studies should investigate the recovery course of behavioral signs of MCS during the acute period as well as the association between the time to emergence of specific behaviors and long-term functional outcome.

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Conflict of interest. None declared

Legends

Figure 1. Participant flow diagram. DoC, Disorders of Consciousness; MCS, Minimally Conscious State; eMCS, emergence from the MCS; CRS-R, Coma Recovery Scale-Revised

Figure 2. Proportion of patients (n=79) presenting each behavior as the first sign of a minimally conscious state. Bars indicate the percentage of the sample that recovered each behavior as the first indication of MCS or eMCS. Visual pursuit (41%), reproducible movement to command (25%) and automatic movement (24%) were commonly observed as the first MCS/eMCS behaviors to emerge. The remaining 10 behaviors emerged first in less than 16% of the sample.

Figure 3. Comparison of behavioral recovery by domain in participants with traumatic brain injury (TBI) and non-TBI. Motor behaviors emerged first significantly more often in the TBI (n=34) versus non-TBI (n=45) group (* p=0.011), with no difference in frequency of recovery of language (p=0.99) or visual (p=0.066) signs of MCS.

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