8 The Chronic Clinical Setting

Vanessa Charland-Verville, Steven Laureys, Olivia Gosseries, Aurore Thibaut, and Marie-Aurélie Bruno

Contents

Abstract

The past 15 years have provided an unprecedented collection of discoveries that have increased our scientific understanding of recovery of human consciousness following severe brain damage. Differentiating between patients in "unresponsive/vegetative" and minimally conscious states still represents a major challenge with profound ethical concerns in terms of medical management. Valid diagnosis is of highest importance in chronic clinical settings, relying on standardized behavioral assessments and neuroimaging paradigms to detect subtle signs of consciousness. An improved assessment of brain function in coma and related states is not only changing nosology and medical care, but also offers a better-documented diagnosis and prognosis and helps to further identify the neural correlates of human consciousness. Recent treatment interventions aimed at accelerating the recovery of awareness show encouraging results, with improvements of behavioral signs of consciousness of severely brain-injured patients. These new insights in this field also raise new legal questions regarding treatment strategies, rehabilitation, and end-of-life decisions.

V. Charland-Verville • M.-A. Bruno • O. Gosseries
A. Thibaut • S. Laureys, MD, PhD (✉)
Coma Science Group, Cyclotron Research Centre and Neurology Department, CHU Sart-Tilman Hospital and University of Liège, Liège 4000, Belgium
e-mail: ma.bruno@ulg.ac.be

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8.1 Disorders of Consciousness

Patients with disorders of consciousness (DOC) represent an important proportion of the disabled population worldwide. Severe brain injury can lead to coma where patients remain unaware with their eyes closed and do not respond to external stimulation (Plum and Posner 1983). When patients open their eyes but remain unconscious, they are diagnosed with vegetative state (VS) (The Multi-Society Task Force on PVS 1994; Laureys and Schiff 2012). The European Task Force on Disorders of Consciousness, recognizing that part of the health care, media, and lay public feels uncomfortable using the unintended denigrating "vegetable-like" connotation (seemingly intrinsic to the term VS), proposed the alternative name "unresponsive wakefulness syndrome" (UWS) (Laureys et al. 2010). UWS is a more neutral and descriptive term, pertaining to patients showing a number of clinical signs (i.e., syndrome) of unresponsiveness (i.e., without response to commands or oriented voluntary movements) in the presence of wakefulness (i.e., eye opening).

Patients who evolve from the UWS/VS condition show nonreflexive, goal-directed behaviors (e.g., visual pursuit, reproducible responses to commands or localisation to pain) and hence are considered to be in a minimally conscious state (MCS) (Giacino et al. 2002). Patients with MCS demonstrate partially preserved fluctuating levels of awareness, but they remain unable to functionally communicate. Depending on the complexity of the demonstrated behaviors, it was recently proposed to subcategorize the MCS condition into MCS- (i.e., when only showing simple nonreflex movements, such as visual pursuit, orientation to pain, or non-contingent behaviors) and MCS+ (i.e., when patients recover the ability to respond to simple commands) (Bruno et al. 2011). Compared to the patients with MCS+, patients with MCS- may suffer from a significant general decrease in brain metabolism in the dominant hemisphere and particularly in regions that are functionally linked to speech comprehension and production, in motor and pre-motor areas and in sensory-motor areas (Bruno et al. 2012). Differential diagnosis for patients with MCS would therefore be mainly due to the functional recovery (or not) of speech-processing areas (Thibaut et al. 2012). Once these patients can communicate in a functional manner and/or show functional object use, they are diagnosed as having emerged from MCS (Giacino et al. 2002). These states lie between unconsciousness and awareness; the distinction between them has important therapeutic and ethical implications (Hirschberg and Giacino 2011). Patients in MCS are more likely to feel pain (Boly et al. 2008; Chatelle et al. 2014a, b) and might benefit from analgesic treatment or other interventions aimed to improve their interaction with the environment (Cruse et al. 2011; Lule et al. 2013; Thibaut et al. 2014). Patients in an MCS are also more likely to recover higher levels of consciousness than are patients with UWS/VS (Luaute et al. 2010; Hirschberg and Giacino 2011). Several countries have established the legal right of physicians to withdraw artificial life support from patients with UWS/VS (Gevers 2005; Perry et al. 2005; Ferreira 2007), but not from patients in a MCS (Manning 2012).

8.2 Behavioral Assessment

The detection of unambiguous signs of consciousness in severely brain-damaged patients is challenging and relies on disentangling automatic responses from nonreflex-oriented movements or command following. Motor responses may be ambiguous and inconsistent, potentially leading to diagnostic errors (Monti et al. 2009). A prospective study on coma survivors showed that the clinical consensus diagnosis of UWS/VS, attributed to 44 patients, was incorrect in 18 cases. Such a high rate of diagnostic error (i.e., 41 %) should prompt clinicians to use validated behavioral scales of consciousness before making the diagnosis of UWS/VS (Schnakers et al. 2009). While consensus-based diagnostic guidelines for DOC have been established (Giacino et al. 2002), there are no procedural guidelines regarding bedside assessment. Many different scales have been developed to assess patients in the chronic phase, and this last decade has particularly been focusing on the differential diagnosis between UWS/VS and MCS. Table 8.1 gives a non-exhaustive overview of the behavioral scales used in the chronic setting.

The American Congress of Rehabilitation Medicine conducted a systematic, evidence-based review of these behavioral assessment scales and provided evidence-based recommendations for clinical use (Seel et al. 2010). It was suggested to use the Coma Recovery Scale-Revised (CRS-R; Giacino et al. 2004; Schnakers et al. 2008a – summarized in Table 8.2). CRS-R has excellent content validity, and it is the only scale to address all Aspen Workgroup criteria (i.e., items used to differentiate MCS from UWS/VS). The CRS-R also offers the advantage to systematically search for signs of nonreflex behavior (e.g., visual pursuit or oriented response to noxious stimulation) and command following, in a well-defined manner. Visual pursuit, for example, should be assessed by using a moving mirror, as it has been shown that a substantial number of patients will not show eye tracking of a moving object or person but will do so when using an auto-referential stimulus such as the own face (Vanhaudenhuyse et al. 2008). Conversely, signs such as visual blinking to threat (Vanhaudenhuyse and Giacino 2008) and visual fixation (Bruno et al. 2010) were shown not to necessarily reflect conscious awareness and could hence be compatible with the diagnosis of UWS/VS. It is important that the evaluations are repeated over time and performed by trained experienced assessors (Lovstad et al. 2010). Confounding factors such as drugs with sedative side effects (e.g., against spasticity or epilepsy) or the presence of infection or other medical complications should be accounted for. This situation is even more problematical when patients have underlying deficits with communication functions, such as aphasia, agnosia, or apraxia (Majerus et al. 2005, 2009). Hence, some behaviorally unresponsive patients could, despite the best clinical assessment, be underestimated in terms of residual cognition or conscious awareness (Giacino et al. 2014). Since the venue of functional neuroimaging, this challenging issue can be addressed by measuring brain activity at rest and during sensory stimulation in these patients (Di Perri et al. 2014; Gosseries et al. 2014a)

8.3 Neuroimaging Assessment

Behavioral scales make inferences about patients' awareness based on (the prensence/absence of) motor responsiveness. Functional neuroimaging (e.g., positron emission tomography (PET) and functional magnetic resonance imaging – fMRI) and cognitive evoked potential studies allow quantifying and noninvasively DOC patients brain activity at rest and during external activation (see Chaps. 9 and 12). fMRI activation studies in UWS/VS (Bekinschtein et al. 2005; Di et al. 2007; Fernandez-Espejo et al. 2008; Coleman et al. 2009) have confirmed previous PET studies showing preserved activation of "lower level" primary sensory cortices which are disconnected from "higher-order" associative cortical networks (i.e., frontoparietal associative cortices, cingulate gyrus, precuneus, and thalamus) (Laureys et al. 2004; Vanhaudenhuyse et al. 2010, 2011; Langsjo et al. 2012; Demertzi et al. 2013) employing auditory (Laureys et al. 2000; Boly et al. 2005), somatosensory (Boly et al. 2008), visual (Owen et al. 2002), or even emotional stimulations (Bekinschtein et al. 2004; Schiff et al. 2005).

These neuroimaging techniques have also been developed in order to detect "neural" (motor-independent) command following. Clinically unresponsive patients could perform mental imagery tasks, as shown by fMRI (Monti et al. 2010). Since this case report, similar "active" or "command following" paradigms have been tested in severe brain-damaged patients with different technologies such as event related potentials or electromyography (Bekinschtein et al. 2008; Schnakers et al. 2008b; Cruse et al. 2011; Habbal et al. 2014). Recently, it has been demonstrated that ^{18}F-fluorodeoxyglucose-PET showed the highest sensitivity in identifying MCS having a good overall congruence with repeated CRS-R diagnosis, when compared to mental imagery task in fMRI (Stender et al. 2014). Complementary to these approaches, methods are developed to detect recovery of consciousness in

Table 8.1 Behavioral scales used in chronic setting

Authors (year)	Scale's name (abbreviation)	Specificity (average execution time in minutes)	Behavioral content (Nb of subscale and nb of items)	Scoring for response	Total score and diagnosis
Giacino et al. (2004)	Coma Recovery Scale-Revised (CRS-R)	Differentiation between UWS/VS and MCS (25)	Auditory, visual, motor, oral, communication, arousal (6 and 23)	"Absent" or "present" (must be reproducible) Varies per item (e.g., at least 3 out of 4 times)	Total score 0–23 0 = coma; 23 = emergence from MCS. UWS/VS, MCS and emergence of MCS diagnosis based on the presence or absence of operationally defined behavioral responses to specific sensory stimulations (e.g., MCS if visual pursuit, responses to command)
Gill-Thwaites and Munday (2004)	Sensory Modality Assessment and Rehabilitation Technique (SMART)	Rehabilitation, differentiation between UWS/VS and MCS (60)	Auditory, visual, tactile, olfactory, gustatory, and motor functions, wakefulness, communication (8 and 8)	5 anchored responses	Each scale score 1–5. 1 = no response, 2 = reflex response, 3 = withdrawal response, 4 = localizing response, 5 = differentiating response MCS or higher if rated a score of 5 on at least one sensory modality on 5 consecutive administrations
Rappaport (2000)	Coma/Near-Coma Scale (CNC)	Post-comatose state, outcome (10)	Visual, auditory, command following, threat response, olfactory, tactile, pain, vocalization (8 and 11)	"Occurs 2–3 times," "occurs 1–2 times" or "does not occur"	Total score 0–44 Average item score: 0.00–0.89 = no coma, 0.90–2.00 = near coma, 2.01–2.89 = moderate coma, 2.90–3.49 = marked coma, 3.50–4.00 = extreme coma
Shiel et al. (2000)	Wessex Head Injury Matrix (WHIM)	Rehabilitation, subtle changes in MCS (30–120)	Basic behaviors, social/communication, attention/cognitive, orientation/memory (62 items)	"Absent" or "present"	Total score 0–62 1 = UWS/VS, 62 = emerging from post-traumatic amnesia

Ansell and Keenan (1989)	Western Neuro Sensory Stimulation Profile (WNSSP)	Rehabilitation, post-comatose state (45)	Auditory comprehension and visual comprehension, visual tracking, object manipulation, arousal/attention, tactile/olfactory (6 and 32)	Varies per items, 3–6 anchored responses	Total score 0–110 maximal Scores between 40 and 50 are generally required for eligibility for rehabilitation. The higher the score, the better
Hagen et al. (1987)	Levels of Cognitive Functioning – Rancho Los Amigos (RLA)	Post-comatose state, outcome (30)	Auditory, visual, motor and oral functions, communication, memory, reasoning, orientation, arousal (8 subscales)	"Absent" or "present"	Total score 1–8 I = no response, II = generalized response, III = localized response, IV = confused/agitated, V = confused/inappropriate, VI = confused/appropriate, VII = automatic/appropriate VIII = purposeful/appropriate

Abbreviations: UWS/VS unresponsive wakefulness syndrome/vegetative state, MCS minimally conscious state

Table 8.2 Summary of the American Congress of Rehabilitation Medicine evidence-based review of behavioral assessment scales for disorders of consciousness (Seel et al. 2010)

Scale	Free access	Guidelines of administration and scoring procedures	Content validity (i.e., enclosing diagnostic criteria)	Internal consistency	Inter-rater reliability	Test-retest reliability	Diagnostic validity	Outcome prediction
Coma Recovery Scale-Revised (CRS-R, Giacino et al. 2004)	Yes	Present	Excellent	Good	Good	Excellent within-subject agreement	Unproven	Not studied
Wessex Head Injury Matrix (WHIM, Shiel et al. 2000)	Yes	Present	Poor	Unproven	Unproven	Unproven	Unproven	Not studied
Western Neuro Sensory Stimulation Profile (WNSSP, Ansell and Keenan 1989)	Yes	Present	Poor	Excellent	Unproven	Unproven	Unproven	Unproven
Sensory Modality Assessment and Rehabilitation Technique (SMART, Gill-Thwaites 1997)	No	Present	Poor	Not studied	Excellent	Excellent within-subject agreement	Unproven	Unproven
Coma Near Coma (CNC, Rappaport 1992)	Yes	Present	Poor	Possibly unacceptable	Unproven	Unproven	Unproven	Not studied

ways that do not depend on the integrity of sensory pathways. Transcranial magnetic stimulation combined with electroencephalography can be performed at the bedside while bypassing subcortical afferent and efferent pathways and without requiring active participation of subjects or language comprehension (see Chap. 10). Hence, this complementary techinique could also permit an effective way to detect and track recovery of consciousness in patients with DOC who are unable to exchange information with the external environment (Rosanova et al. 2012, Casali AG et al. 2013 and Sarasso S et al. 2014). The validation of new promising neuroimaging-based differential diagnostic markers, such as quantified metabolic markers or resting state fMRI, is of primary importance to complement the differential diagnosis.

8.4 Treatment

Although our understanding of the neural correlates of consciousness has greatly evolved over the past years, daily care has not yielded specific, evidence-based medical treatments for patients with DOC. Pharmacological treatment to promote the emergence of consciousness can be administered in the subacute and the chronic (more than 1 month) phases. Frequently prescribed pharmacological treatments include dopaminergic (e.g., amantadine, apomorphine, methylphenidate, levodopa, bromocriptine) and GABAergic agents (e.g., zolpidem, baclofen) (Chew and Zafonte 2009; Gosseries and Charland-Verville, 2014; Thonnard et al. 2014). Next, there is a long history of brain stimulation in medical science, and research has long been focused on some cortical areas and deep brain structures like the prefrontal cortex and the thalamus. Only few techniques were studied scientifically in this population of patients. Deep brain stimulation showed behavioral improvement after the implantation of an electrical stimulator in the intralaminar nuclei (Schiff et al. 2009). However, and the number of patients who can benefit from this intervention is still limited. Recently, noninvasive transcranial direct current stimulation (tDCS) studies showed encouraging results, with improvements in the behavioral signs of consciousness of severely brain-injured patients (Thibaut et al. 2014). Short-duration anodal (i.e., excitatory) tDCS of left dorsolateral prefrontal cortex induced short-term improvement in patients with MCS of acute and chronic etiologies measured by behavioral CRS-R total scores. The long-term noninvasive neuromodulatory tDCS outcome clinical improvement remains to be shown. In the years to follow, interventions should multiply, and therapeutic measures need to be more accessible, controlled, and effective.

8.5 Ethical Challenges

Early since DOC appeared in the clinical setting, clinicians, scholars, theologians, and ethicists began to wonder how it is like to be in a state of altered consciousness (e.g., Thompson 1969). First, one of the most debatable issues about this population is pain perception. Painful experience is a first-person one and classic pain assessment requires the patients' verbal feedback (International Association of Pain Specialists (IASP 1994)). When it comes to severely brain-injured patients who are unable to communicate their feelings and possible suffering, the question of pain perception is far more complex (Chatelle et al. 2014a, b). According to survey attitudes among healthcare professionals to the question "Do you think that patients in a UWS/VS can feel pain?" 68 % of the interviewed paramedical caregivers ($n=538$) and 56 % of physicians ($n=1166$) answered "yes." Paramedical professionals, religious caregivers, and older caregivers reported more often that UWS/VS patients might experience pain. Following professional background, religion was the highest predictor of caregivers' opinion: 64 % of religious ($n=1{,}009$; 850 Christians) versus 52 % of nonreligious respondents ($n=830$) answered positively. To the question "Do you think that patients with MCS can feel pain?" nearly all interviewed caregivers answered "yes" (96 % of the medical doctors and 97 % of the paramedical caregivers). Women and religious caregivers reported more often that MCS patients might experience pain (Demertzi et al. 2009). Considering these results on varying beliefs about pain perception in DOC, physicians and health-care workers' views on analgesia and symptom management may also be affected. The presence or absence of nociception is inferred via motor responses following noxious stimulation, such as stereotypical responses, flexion withdrawal, and localization responses (Schnakers and Zasler 2007). In patients with DOC, only a clear localization to noxious stimulation is considered to be an indicator of conscious perception (Giacino et al. 2002). In order to accurately nonverbally assess nociception in this challenging population, the Nociception Coma Scale-Revised (NCS-R) (Chatelle et al. 2012) has been proposed. It assesses motor, verbal, and facial behaviors behavioral responses at rest, during daily nursing care, and during nociceptive stimulation. A cut-off score of 4 and higher suggest the need of adequate pain management (Chatelle et al. 2014a, b).

Patients with chronic DOC may also pose ethical challenges requiring the mediation of legal authorities in order to regulate end-of-life decisions. When the clinical condition of a patient has been stabilized and denoted as irreversible, decisions about artificial nutrition and hydration limitation may come into play. In a European survey, the controversies around the clinical management at the end-of-life were reflected (Demertzi et al. 2011). Sixty-six percent of health-care professionals agreed to withdraw treatment in patients with UWS/VS for more than 1 year, whereas only 28 % agreed to do so for patients with MCS. In our study, we also found that end-of-life decisions are not always governed by clinical circumstances but rather, physicians' characteristics. Geographic differences as well as religious background were the variables that consistently predicted end-of-life statements. Residents from Northern and Central Europe, as compared to Southern Europeans, were more likely to agree with medically assisted nutrition and hydration withdrawal in chronic (> 1 year) UWS/VS, whereas religious respondents, older respondents, and women were less likely to find it acceptable. From a bioethical standpoint, withdrawing artificial nutrition and hydration is comparable to withdrawing mechanical ventilation, even if emotionally these two actions may be perceived differently (Laureys 2005). Despite the controversy as to whether artificial nutrition and hydration constitutes a medical treatment (Bernat and Beresford 2006), most of the medical community would agree with its being a medical therapy which can be refused by patients and surrogate decision makers (Steinbrook and Lo 1988). Patients with DOC represent a difficult group, ethically, for surrogate decision-making. The medical community needs policies to reach better internal agreement within the professional network and effective communication with patient communities and their families (Manning 2012; Bruno et al. 2013).

8.6 Conclusion

Disentangling between patients with MCS and UWS/VS represents a major challenge that can have heavy consequences, generating ethical and legal implications (Celesia 2000; Jennett 2002). The rapidly growing scientific findings on DOC must be taking into account for patients' future care needs and to promote adequate policies to keep up with the findings. Consciousness research leads to redefinition of recovery, clinical criterion for diagnosis, and as increasing impact on prognosis (Fins 2009). The constantly evolving neuroimaging research field is raising new questions and challenges for medical ethics. As a result, clinicians must increasingly answer requests from family members and surrogate decision makers about the new diagnostic and therapeutic procedures. Because most of these reported procedures remain investigational, clinicians must be aware of the level of evidence supporting them and of the unavoidable ethical and social issues involved in responding to such requests. Moreover, studies must be supported in order to address the sensitivity and specificity of the neuroimaging or electrophysiological tools. Multicentric studies and collaborative work seem also essential to gather comparable data for the clinical behavioral assessments and about the potential prognostic value of the neuroimaging technologies (Di et al. 2008; Coleman et al. 2009).

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