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Detecting signs of consciousness in severely brain injured patients recovering from coma

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Abstract

The number of patients who survive severe acute brain injury increased dramatically in the last few years generating social, economical and ethical challenges. Nevertheless, detecting behavioral signs of consciousness is currently really difficult in patients with limited behavioral repertoires and often complicated by inconsistent or easily exhausted motor responses. An error of diagnosis can lead to inadequate care management (e.g., pain treatment) and/or inappropriate end-of-life decision. In this review, we will present information about diagnostic criteria, prognosis and remnant brain processing in the main disorders of consciousness. We will also discuss standardized behavioral scales which have been developed to facilitate the assessment of consciousness in patients recovering from coma.

The number of patients who survive severe acute brain injury increased dramatically in the last few years generating social, economical and ethical challenges (Jennett, 2005). Even if a majority of severely brain injured patients recover from coma within the first two weeks after the insult, others will take more time and go through different stages before fully or partially recovering consciousness. Detecting behavioral signs of consciousness is currently the main way to distinguish conscious from unconscious patients. The diagnosis of consciousness level is nevertheless really difficult to make in patients with limited behavioral repertoires and often complicated by inconsistent or easily exhausted motor responses. Misdiagnosis has consequently been reported as being really frequent (Childs et al., 1993; Andrews et al., 1996; Schnakers et al., 2009). Moreover, an error of diagnosis can lead to inadequate care management (e.g., pain treatment) and/or inappropriate end-of-life decision. For these reasons, knowing information about diagnostic criteria, prognosis but also remnant brain processing of each disorder of consciousness can help in making the diagnosis. Furthermore, standardized behavioral scales have been developed to facilitate the assessment of consciousness in patients recovering from coma (Majerus et al., 2005; Gill-Twaithes, 2006). In this paper, we will review the three major disorders of consciousness (i.e., the coma, the vegetative state and the minimally conscious state) encountered in clinical practice and we will disentangle them from other states such as the locked-in syndrome and brain death (see

Table 1). We will then discuss behavioral assessment procedures designed for their use at the bedside, focusing on those which are well validated.

Disorders of consciousness

Coma

Plum and Posner defined coma as a pathological state related to severe and prolonged dysfunction of vigilance and consciousness (Plum and Posner, 1966). This state results from global brain dysfunction (most often due to diffuse axonal injury following traumatic brain injury), or from a lesion limited to brainstem structures involving the reticular activating system. The distinguishing feature of coma is the continuous absence of eye-opening (spontaneously or following stimulation). There is no evidence of visual fixation or pursuit, even after manual eye-opening. No voluntary motor behavior is observed and behavioral responses are limited to reflex activity only. Electrical activity is observed, albeit characterized by slow frequency bands (i.e., mostly delta and theta activity) (Young, 2000; Brenner, 2005). Positon Emission Tomography (PET scan) studies have also shown a 40 to 50 % reduction of overall brain metabolism in traumatic or hypoxic coma (Laureys et al., 2004). This state must last at least one hour to be differentiated from a transient disorder of consciousness (e.g., syncope, confusion or delirium). Prolonged coma is rare. Usually, coma resolves within 2 to 4 weeks, most often evolving into VS or MCS (Attia and Cook, 1998). Traditional electroencephalographic (EEG) measures have shown their efficacy in predicting outcome after anoxic or traumatic brain damage (Young, 2000; Brenner, 2005). However, recent studies have shown that somatosensory evoked potentials (N20) and mismatch negativity (MMN) have predictive value superior to EEG, a bilateral absence of the N20 or MMN response in comatose patients being strongly associated to absence of full recovery (respectively, 99-100% of cases and 91-93% of cases) (Amantini et al., 2005; Fischer et al., 2006).

Vegetative state

The term “vegetative” suggests a preservation of autonomic functions (e.g., cardio-vascular, respiratory and thermoregulation functions) and reemergence of the sleep-wake cycle (i.e., periods of spontaneous eyes opening). VS often results from trauma-induced bi-hemispheric injury involving the white matter or from bilateral lesions in the thalamus with sparing of the brainstem, hypothalamus and basal ganglia (Giacino, 1997). Behaviorally, there is no response to verbal order and, although moaning may occur, there is no intelligible speech (The Multi-Society Task Force on PVS, 1994). Infrequently, behaviors such as inappropriate smiling, crying or grimacing, and even randomly-produced single words have been reported in patients diagnosed with VS (Working Party of the Royal College of Physicians, 2003). With careful assessment, it is possible to demonstrate that these behaviors are not voluntary or goal-directed. Functional neuroimaging studies show a severe reduction of brain metabolism in the fronto-temporo-parietal network with activation limited to primary cortices after auditory or noxious stimulation, suggesting the absence of integrated brain processing (Laureys and Boly, 2007). Establishing a definitive prognosis is difficult, however, when this state lasts one month or more, the patient is considered in “persistent” VS. When VS lasts more than 3 months (for non-traumatic etiologies) or one year (for traumatic etiology), the patient can be considered in “permanent” VS (The Multi-Society Task Force on PVS, 1994). In view of lingering uncertainty about prognostic indicators and well-documented cases of late recovery (Childs and Mercer, 1996), the American Congress of Rehabilitation Medicine (1995) has recommended that the term “permanent VS” be abandoned in favor of documenting the cause of the VS (e.g., traumatic brain injury, stroke or anoxia) and the length of time post-onset as both carry prognostic information .

Minimally conscious state

The minimally conscious state is characterized by the presence of inconsistent but clearly-discernible behavioral signs of consciousness (Giacino et al., 2002). Such signs must be reproducible within a given examination, although behavior may fluctuate across examinations. In contrast to patients in VS who may display random episodes of crying or smiling, these behaviors are contingent upon appropriate environmental triggers in MCS. Early reemergence of visual pursuit appears to be a behavioral marker of the transition from VS to MCS (Giacino and Whyte, 2005). Functional neuroimaging studies have shown large regions of fronto-temporo-parietal activation after auditory or noxious stimulation as well as intact connectivity between primary and associative cortices suggesting greater preservation of distributed neural processing (Laureys and Boly, 2007). Regarding prognosis, the probability of functional recovery at one year following traumatic brain injury is significantly more favorable relative to VS (50% vs. 3% attaining moderate disability). Some patients in MCS progress slowly while others remain in this condition permanently (Fins et al., 2007). It is also important to recognize that, unlike VS, clearly-defined temporal parameters for recovery do not exist (Lammi et al., 2005), and there is wide heterogeneity in the degree of functional recovery ultimately attained. *Emergence from MCS* occurs when the patient is able to reliably communicate through verbal or gestural yes-no responses, or is able to demonstrate use of two or more objects (e.g., hairbrush, cup) in a functional manner (Giacino et al., 2002).

Differential Diagnosis

Locked-in syndrome

The locked-in syndrome (LIS) is marked by tetraplegia and anarthria in the setting of near-normal to normal cognitive function (American Congress of Rehabilitation Medicine, 1995). This state is caused by a lesion involving the ventral pons and, in 60% of cases, is due to basilar thrombosis. Because patients with LIS have spontaneous eyes opening, but are unable to speak or move the extremities, this state can easily be confused with VS. On average, the diagnosis of LIS is not established until 2.5 months post-onset. There is evidence that family members tend to detect signs of consciousness (55% of cases) prior to medical staff (23% of cases) (Laureys et al., 2005). Classic LIS consists of complete paralysis of the orobuccal musculature and all four extremities. However, vertical eye movements, which allow non-verbal communication through directional gaze, are spared. Perceptual functions are also spared as ascending afferent axons remain intact (American Congress of Rehabilitation Medicine, 1995). Bauer has described multiple varieties of LIS, including the incomplete form in which there is residual motor activity (frequently, finger or head movement), and total LIS, in which there is complete immobility including both horizontal and vertical eye movements (Bauer et al., 1979). Functional neuroimaging typically shows preserved supra-tentorial areas with hypometabolism in the cerebellum, a structure closely linked to coordinated motor activity). Interestingly, significant hyperactivity has been observed bilaterally in the amygdala of acute LIS patients, likely reflecting anxiety generated by the inability to move or speak (stressing the importance of appropriate anxiety treatment soon after diagnosis) (Laureys et al., 2005). The presence of a relatively normal and reactive electroencephalographic rhythm after a brainstem lesion should alert the physician, but heterogeneity of EEG findings suggests that this approach cannot per se disentangle LIS from disorders of consciousness (Bassetti and Hess, 1997). Data on life expectancy suggest that some patients with LIS patients live twelve or more years post-onset. Surprisingly, LIS patients rate their quality of life similarly to the healthy population (Bruno et al., 2009). In the absence of other structural or functional brain abnormalities (Smart et al., 2008), patients with LIS are generally able to make independent decisions and communicate their preferences (Schnakers et al., 2008).

Brain death

Brain death is a condition in which there is "irreversible unconsciousness with complete loss of brain function". It is marked by the presence of apnea and the lack of any behavioral response to the environment (Medical Consultants on the Diagnosis of Death, 1981). Generally, an electroencephalogram demonstrates electrocerebral silence reflecting the absence of electrical brain activity. Transcranial doppler studies reveal the absence of cerebral blood flow. Finally, functional imaging, using cerebral perfusion tracers and single photon emission tomography (SPECT), illustrate the “empty skull” sign in which the “whole brain” (Facco et al., 1998) is inactive. After excluding brain dysfunction due to drug toxicity or hypothermia, a final diagnosis can be established after 6 to 24 hours.

Behavioral assessment

Consciousness

Behavioral observation constitutes the standard method for detecting signs of consciousness in severely brain injured patients. It is important, however, to make a distinction between “arousal” and “consciousness”. Indeed, a patient can be aroused but show no signs of consciousness, as in VS. Preservation of arousal is therefore a necessary but insufficient condition for consciousness (see Fig 1). Moreover, consciousness should not be viewed as a dichotomous phenomenon but rather as a continuum. It is possible, for example, for a patient in coma to rapidly evolve into VS, gradually transition to MCS, and subsequently lapse back into coma.

Misdiagnosis

Differentiating between MCS and VS can be challenging. The detection of voluntary behaviors is often difficult and signs of consciousness can easily be missed due to sensory and motor disabilities, tracheostomy, fluctuating arousal levels or ambiguous and rapidly exhausted responses (Majerus et al., 2005). Previous studies have shown that 37 to 43 % of patients with disorders of consciousness are erroneously diagnosed with VS (Childs et al., 1993; Andrews et al., 1996). Since, other reports concerning the diagnostic criteria for VS and MCS (Giacino et al., 2002; Working Party of the Royal College of Physicians, 2003) have suggested lower misdiagnosis estimates (Jennett, 2005). A more recent study, however has again reported a misdiagnosis rate of 41%, consistent with the earlier evidence (Schnakers et al., 2009). Misdiagnosis among patients with disorders of consciousness has hence not substantially changed. An accurate diagnosis is nevertheless crucial not only for daily management (particularly, pain treatment) and end-of-life decisions, but also has prognostic implications as patients in MCS have more favorable functional outcomes as compared to those in VS. Schnakers and coworkers (2009) suggest that the systematic use of a sensitive standardized neurobehavioral assessment scale may help decrease diagnostic error and limit diagnostic uncertainty.

Behavioral scales

Numerous behavioral rating scales have been developed and validated to assess level of consciousness and establish diagnosis (Majerus et al., 2005). In this section, we briefly review instruments commonly used in the acute and rehabilitation settings.

The *Glasgow Coma Scale* (GCS) remains the most widely used scale in trauma and acute care settings. The GCS was the first validated rating scale developed to monitor level of consciousness in the intensive care unit (Teasdale and Jennett, 1974). This scale is relatively brief and can easily be incorporated into routine clinical care. It includes three subscales that address arousal level, motor function and verbal abilities. Subscales scores are added and yield a total score ranging from 3 to 15. Despite its widespread use, the GCS has been criticized for variable inter-rater agreement and problems deriving scores in patients with ocular trauma, tracheostomy or ventilatory support (McNett, 2007).

The *Full Outline of UnResponsiveness scale* (FOUR) was recently developed to replace the Glasgow Coma Scale to assess severely brain-injured patients in intensive care (Wijdicks, 2006; Wijdicks et al., 2005). The scale is comprised of four subscales assessing motor and ocular responses, brainstem reflexes and breathing. The total score ranges from 0 to 16. Unlike the GCS, the FOUR does not assess verbal functions to accommodate the high number of intubated patients in intensive care. A score of 0 on the FOUR assumes the absence of brainstem reflexes and breathing and, therefore, helps to diagnose brain death. The scale also monitors recovery of autonomic functions and tracks emergence from VS. The FOUR is specifically designed to detect patients with locked-in syndrome as it uses oculomotor commands that exploit vertical eye movements and eye blinks, both of which are preserved in LIS.

The *Wessex Head Injury Matrix* (WHIM) (Shiel et al., 2000) was developed to capture changes in patients in VS through emergence from post-traumatic amnesia. This tool is particularly sensitive to detecting changes in patients in MCS not captured by traditional scales such as the GCS (Majerus and Van der Linden, 2000). Shiel and collaborators longitudinally followed 97 severely brain injured patients recovering from coma to create the WHIM. WHIM items were ordered according to the sequence of recovery observed in these patients. The 62-item WHIM’s six sections assess arousal level and concentration, visual consciousness (i.e., visual pursuit), communication, cognition (i.e., memory and spatiotemporal orientation) and social behaviors. The WHIM score represents the rank of the most complex behavior observed.

The *Sensory Modality Assessment and Rehabilitation Technique* (SMART) (Gill-Thwaites, 1997) was developed to identify signs of consciousness observed during “sensory stimulations programs” intended to support cerebral plasticity and improve level of consciousness (Wood, 1991). The SMART assesses 8 modalities including visual, auditory, tactile, olfactory and gustatory sensation, motor functions, communication and arousal level. The SMART is a hierarchical scale consisting of 5 response levels (‘absence of response’ – Level 1; 'reflex response' – Level 2; ‘ withdrawal response’ – Level 3; ‘localization response’ – Level 4; ‘discriminative response’ – Level 5). The SMART has previously been shown to have very good validity and reliability in a population of 60 patients diagnosed as being in a vegetative state or in a minimally conscious state (Gill-Thwaites and Munday, 2004).

The JFK *Coma Recovery Scale* was originally developed by investigators from the JFK Johnson Rehabilitation Institute in 1991 (Giacino et al., 1991). The scale was revised and republished in 2004 as the JFK Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004). The purpose of the CRS-R is to assist with differential diagnosis, prognostic assessment and treatment planning in patients with disorders of consciousness. The scale consists of 23 items that comprise six subscales addressing auditory, visual, motor, oromotor, communication and arousal functions (see Table 2). CRS-R subscales are comprised of hierarchically-arranged items associated with brain stem, subcortical and cortical processes. The lowest item on each subscale represents reflexive activity while the highest items represent cognitively-mediated behaviors. Scoring is standardized and based on the presence or absence of operationally-defined behavioral responses to specific sensory stimuli. Psychometric studies indicate that the CRS-R meets minimal standards for measurement and evaluation tools designed for use in interdisciplinary medical rehabilitation. Adequate interrater and test-retest reliability have been established indicating that the CRS-R can be administered reliably by trained examiners and produces reasonably stable scores over repeated assessments. Validity analyses support use of the scale as an index of neurobehavioral function and have shown that the CRS-R is capable of discriminating patients in MCS from those in VS which is of critical importance in establishing prognosis and formulating treatment interventions (Schnakers et al., 2006; Schnakers et al., 2008; Vanhaudenhuyse et al., 2008). Spanish, Portuguese, Italian, German, French, Dutch, Norwegian and Danish translations of the CRS-R are available.

Conclusion

Patients with severe disorders of consciousness present significant diagnostic, prognostic and everyday management problems. Recovery of consciousness is usually very gradual, sometimes marked by emergence of clear behavioral milestones, but more often by subtle improvements. There are frequent fluctuations in both arousal and awareness, and sometimes, there are setbacks. Subtle signs of consciousness have to be recognized early to avoid misdiagnosis. Bedside assessment of residual cognitive functions is often difficult due to insufficient arousal level, motor impairment, fluctuating responses, sedation or other confounding factors. Knowledge of medically-accepted diagnostic criteria and reliance on validated behavioral assessment scales are crucial for establishing accurate diagnosis, prognostic and management decisions (including end-of-life).

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Figures and Tables

Table 1: Diagnostic criteria for brain death, coma, vegetative and minimally conscious states and locked-in syndrome

Consciousness level	Diagnostic criteria	Reference(s)
Brain death	• No arousal/eye-opening • No behavioral signs of awareness • Apnea • Loss of brain functions (brainstem reflexes)	Medical Consultants on the Diagnosis of Death, 1981
Coma	• No arousal/eye-opening • No behavioral signs of awareness • Impaired spontaneous breathing • Impaired brainstem reflexes • No vocalizations > 1 hour	Plum & Posner, 1966
Vegetative state	• Arousal/stpontaneous or stimulus-induced eye opening • No behavioral signs of awareness • Preserved spontaneous breathing • Preserved brainstem reflexes • No purposeful behaviors • No language production of comprehension • Preservation (partial or complete) of hypothalamic and brain stem autonomic functions • > 1 month: persistent vegetative • Compatible: grimaces to pain, localization to sounds • Atypical but compatible: visual fixation, response to threat, inappropriate single words	The Multi-Society Task Force on PVS, 1994 Working Party of the Royal College of Physicians, 2003
Minimally conscious state	• Arousal/spontaneous eye-opening • Fluctuating but reproducible behavioral signs of awareness • Response to verbal order • Environmentally-contingent smiling or crying • Object localization and manipulation • Sustained visual fixation and pursuit • Verbalizations • Intentional but unreliable communication • Emergence from MCS: functional communication, functional object use	Giacino et al, 2002
Locked-in syndrome	• Arousal/spontaneous eye-opening • Preserved cognitive functions • Communication vis eye gaze • Anarthria • Tetraplegia	American Congress of Rehabilitation Medicine, 1995

Figure 1

Behavioral observation assesses two dimensions of consciousness: arousal and awareness. In brain death and coma, both dimensions are absent. In the vegetative state, arousal level is relatively preserved in the absence of signs of awareness. In the minimally conscious state, both dimensions are present although behavioral signs often fluctuate. In the locked-in syndrome, both dimensions are fully preserved despite complete loss of speech and motor functions.

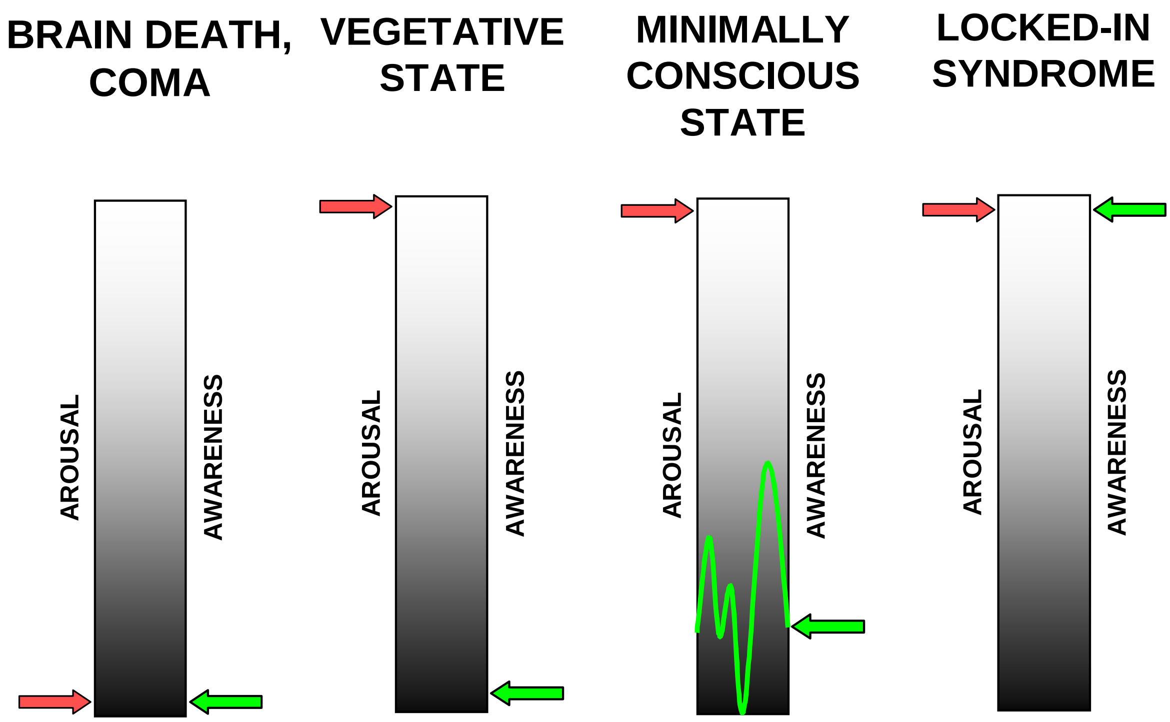

Table 2 : CRS-R Response Profile

AUDITORY FUNCTION SCALE
4 - Consistent Movement to Command *
3 - Reproducible Movement to Command *
2 - Localization to Sound
1 - Auditory Startle
0 – None
VISUAL FUNCTION SCALE
5 – Object Recognition *
4 – Object Localization: Reaching *
3 - Pursuit Eye Movements *
2 – Fixation *
1 – Visual Startle
0 – None
MOTOR FUNCTION SCALE
6 - Functional Object Use [t]
5 - Automatic Motor Response *
4 – Object Manipulation *
3 - Localization to Noxious Stimulation *
2 - Flexion Withdrawal
1 - Abnormal Posturing
0 - None/Flaccid
OROMOTOR/VERBAL FUNCTION SCALE
3 - Intelligible Verbalization *
2 - Vocalization/Oral Movement
1 - Oral Reflexive Movement
0 – None
COMMUNICATION SCALE
2 - Functional: Accurate [t]
1 - Non-Functional: Intentional *
0 – None
AROUSAL SCALE
3 - Attention *
2 - Eye Opening w/o Stimulation
1 - Eye Opening with Stimulation
0 - Unarousable

Denotes MCS *; Denotes emergence from MCS [t]

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