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Clinical assessment of patients with disorders of consciousness

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ABSTRACT

The study of pathological impairments of consciousness, as they can appear in severely brain injured patients, can be particularly useful to better clarify cognitive processes and cerebral substrates which underlie consciousness. In this review, we will introduce the disorders of consciousness that can be presented by severely brain-injured patients and the behavioural scales that can be used to assess their level of consciousness. We will also discuss the difficulty to assess and detect remnant cognitive functioning in these patients.

Key words

Brain injury • Consciousness • Brain death • Coma • Vegetative state • Minimally conscious state

Introduction

The study of pathological impairments of consciousness, as they can appear in severely brain injured patients, can be particularly useful to better clarify cognitive processes and cerebral substrates which underlie consciousness. The vegetative state is characterized by a preservation of the arousal level but also by the absence of any sign of consciousness of the environment and of oneself (e.g., absence of oriented responses to sensory stimulations or absence of significant verbal production) (The Multi-Society Task Force, 1994). The patient in a minimally conscious state, on the contrary, demonstrates inconsistent, primary but reproducible signs of consciousness of the environment (e.g., visual pursuit of an object moving in the patient's visual field) and of oneself (e.g., accurate response to verbal order suggesting an interaction between the patient and his/her surroundings) (Giacino et al., 2002). Both populations mentioned here are therefore particularly useful to study the concept of consciousness via the progressive recovery of the most basic aspects of consciousness, and the behavioural, cognitive and cerebral signs which accompany them. In this review, we will introduce the disorders of consciousness that can be presented by severely brain-injured patients and the behavioural scales that can be used to assess their level of consciousness. We will also discuss the difficulty to assess and detect remnant cognitive functioning in these patients.

Disorders of consciousness: definition

Brain death

Brain death suggests that the organism cannot function as a whole (Medical Consultants on the Diagnosis of Death, 1981). Critical functions such as respiration and circulation, neuroendocrine and homeostatic regulation, and consciousness are permanently absent. The patient is apneic and unreactive to environmental stimulation (Fig. 1). The term "brain death" requires the bedside demonstration of irreversible cessation of all clinical functions of the brain, but also, of the brainstem. Brain death is classically caused by a brain lesion (for example,

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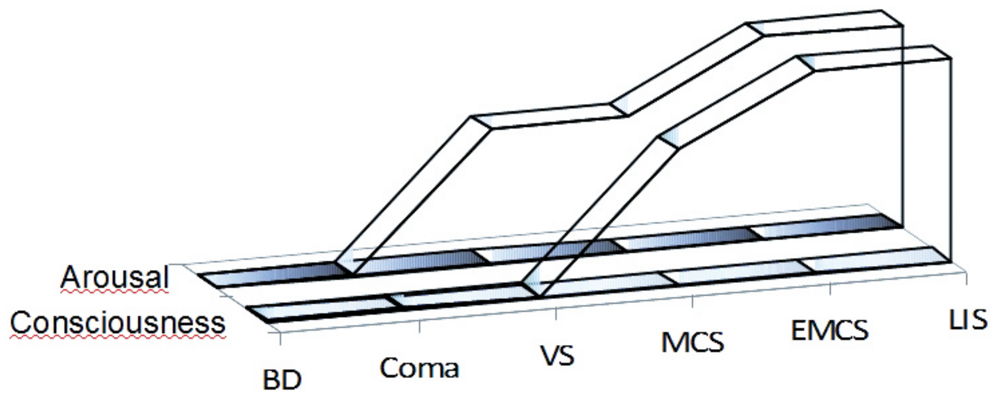

Fig. 1. - Arousal and consciousness level in each disorder of consciousness (i.e., brain death – BD, coma – C, vegetative state – VS, minimally conscious state – MCS), emergence from minimally conscious state – EMCS and in locked-in syndrome – LIS.

massive traumatic injury, intracranial haemorrhage or anoxia) that results in an intracranial pressure higher than the mean arterial blood pressure. After excluding the impact of pharmacological (or toxic) treatments or hypothermia, the diagnosis can be done within 6-24 hours (Powner, 2009).

Coma

If they survive, patients can stay in a coma for several weeks, being neither aroused, nor aware; indeed, their eyes are constantly closed and they do not manifest voluntary behavioral responses (Plum and Posner, 1966) (Fig. 1). Generally, patients emerge from their comatose state within 2 to 4 weeks. The prognosis is influenced by different factors such as etiology, the patient's general medical condition and age. Outcome is known to be bad if, after 3 days of observation, there are no pupillary or corneal reflexes, stereotyped or absent motor response to noxious stimulation, iso-electrical or burst suppression pattern EEG. Prognosis in traumatic coma survivors is better than in anoxic cases. Recovery from coma may lead to a vegetative state, a minimally conscious state or, more rarely, to a locked-in syndrome (Tshibanda et al., 2010).

Vegetative state

The term "vegetative state" (VS) was defined to describe "an organic body capable of growth and development but devoid of sensation and thought". This state implies the preservation of autonomic functions (e.g., cardio-vascular regulation, thermoregulation) and the sleep-wake cycle with the absence of awareness (Fig. 1). Behaviorally, patients in VS open their eyes spontaneously or in response to stimulation, but they only show reflex behaviors, unrelated to the environment (The Multi-Society Task Force, 1994). It is very important to stress the difference between persistent and permanent VS which are, unfortunately, too often abbreviated identically as PVS, causing unnecessary confusion. When the term "persistent vegetative state" was first described, it was emphasized that persistent did not mean permanent and it is now recommended to omit "persistent" and to describe a patient as having been VS for a certain period of time. When there is no recovery after a specified period (depending on etiology, three to twelve months) the state can be declared permanent and, only then, the ethical and legal issues around withdrawal of treatment can be discussed (Monti et al., 2010a). Nevertheless, regarding the negative associations intrinsic to the term "vegetative state", it has been recently proposed to rather use the term: unresponsive wakefulness syndrome (Laureys et al., 2010).

Minimally conscious state

Patients in a minimally conscious state (MCS) are awake and show fluctuating but reproducible signs of awareness (Giacino et al., 2002) (Fig. 1). These patients can manifest emotional and oriented behavioral responses such as response to verbal order, object manipulation, oriented responses to noxious stimulation, visual pursuit or fixation. However, these behaviors can fluctuate in time, which makes challenging the detection of awareness. Recovery from MCS is defined by the emergence of a functional communication and/or functional objects use (Giacino et al., 2002). Even if prognosis is better as compared VS, some patients can remain in a MCS without fully recovering consciousness for a prolonged period of time (Fins et al., 2007).

Locked-in syndrome

Even if it is not an altered state of consciousness, the Locked in Syndrome (LIS) has to be mentioned as it may present the same behavioral pattern than what is observed in VS. Misdiagnosis can therefore easily occurred (American Congress of Rehabilitation Medicine, 1995). Indeed, LIS patients cannot move or talk but are able to use vertical eye movements and blinking to communicate with their surroundings. This syndrome is often due to a selective supranuclear motor de-efferentation producing a paralysis of all four limbs and the last cranial nerves without interfering with consciousness or cognition (Fig. 1). According to Bauer et al. (1979), different categories of LIS can be based on the extent of motor impairment: *Classical* LIS consists of a total immobility but preserved vertical eye movements and blinking; *Incomplete* LIS is characterized by remnant non-ocular voluntary motions (e.g., head or fingers movements); *total* LIS patients are completely immobile, unable to control any eye movements.

Behavioral scales

Differentiating MCS from 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. A recent study has shown that 41% of patients with disorders of consciousness are erroneously diagnosed with VS (Schnakers et al., 2009a). An accurate diagnosis is 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. Numerous behavioral rating scales have been developed and validated to assess level of consciousness and establish accurate 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)

The 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)

The FOUR was recently developed to replace the GCS to assess severely brain-injured patients in intensive care (Wijdicks et al., 2005). The scale includes 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 detect vertical eye movements and eye blinks, both being preserved in LIS.

The Wessex Head Injury Matrix (WHIM)

The 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 et al. longitudinally followed 97 severely brain injured patients recovering from coma to create the WHIM. The 62-items were ordered according to the sequence of recovery observed in these patients and 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)

The 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. 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 VS or in a MCS (Gill-Thwaites and Munday, 2004).

The JFK Coma Recovery Scale (CRS-R)

The CRS-R was originally developed by investigators from the JFK Johnson Rehabilitation Institute in 1991 (Giacino et al., 1991). The scale was revised and published 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 (Table I). 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 (Seel et al., 2010).

Consciousness, cognition and behavioral assessment

It is widely accepted that consciousness is a multicomponent concept (Baars et al., 2003; Cleeremans, 2003; Zeman, 2005). First, consciousness can be considered as a 'state of arousal'. Here we consider a continuum from coma to full arousal. It is important, however, to make a distinction between arousal and consciousness. Indeed, a patient can present an intact arousal level (and, hence, at a behavioural level, a sustained eye opening) but show no signs of consciousness, as it is the case in the VS patients (Fig. 1). Preservation of arousal is therefore a necessary but insufficient condition for consciousness. On the other hand, we can see consciousness as information treated by our sensory systems leading to perception: 'the consciousness of the environment'. Finally, we can consider 'self-awareness'; this aspect of consciousness represents, at the most basic level, the capacity which has an individual to voluntarily respond to a stimulation directed to himself. Using a behavioral scale, the consciousness level will be assessed using various stimuli (e.g., auditory, visual or motor) in order to detect oriented responses, and, hence, conscious activity. These stimuli mainly allow the evaluation of the relative preservation of sensory pathways and the way the patient basically interact/respond to these stimulations. These scales do not directly give precise information on the cognitive components involved in consciousness processing. Indeed, consciousness requests the intervention of basic cognitive functions allowing appropriate interaction with the environment. A conscious experience requires a series of cognitive processes such as attention and

Table I. - Protocol of the Coma Recovery Scale - Revised (CRS-R).

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†
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
3 - Oriented†
2 - Functional: Accurate†
1 - Non-Functional: Intentional*
0 - None
AROUSAL SCALE
3 - Attention*
2 - Eye Opening w/o Stimulation
1 - Eye Opening with Stimulation
0 - Unarousable

* indicates minimally conscious state; † indicates emergence from minimally conscious state.

memory (e.g., working memory which allows us to temporarily maintain and manipulate information) (Baars et al., 2003). Indeed, in order to be conscious, an individual must focus his/her attention on the environment and/or oneself, select pertinent stimuli and react adequately. The voluntary and selective orientation of attention seems therefore to play an important role in consciousness processing. High-order cognitive system such as working memory is also primordial. It allows to manage a large amount of information at the same time, to choose and to plan appropriate behaviours as a function of the requirements of the environment. Main behaviors considered as being conscious required these cognitive components. It is nevertheless difficult to assess attention and working memory using existing behavioral scales. Until now, residual cognitive processes in patients recovering from coma were often studied by using paramedical techniques such as electrophysiology or neuroimagery.

Mainly, these techniques used 'passive' paradigms in which subjects do not have to actively perform a task. The majority of these paradigms were testing basic sensory processing using visual (e.g., Menon et al., 1998), somatosensory (e.g., Laureys et al., 2002; Kassubek et al., 2003; Boly et al., 2008) or auditory stimuli (e.g., Boly et al., 2004; Laureys et al., 2004 for neuroimagery and Kane et al., 2000; Daltrozzo et al., 2007 for electrophysiology). These stimuli did not request higher-order cognitive processing but at best a good arousal level. Others studies assessed more complex processing such as speech processing (Laureys et al., 2004; Bekinschtein et al., 2004; Schiff et al., 2005; Perrin et al., 2006). Speech processing can nevertheless be observed in anesthesia suggesting it does not require consciousness (Davis et al., 2007). Interestingly, among these studies, Laureys (2004) and Perrin (2006) used the own name which is usually related to selective attentional processing (i.e., cocktail party phenomenon) (Wood and Cowan, 1995). Perrin et al. (2006) showed a larger P3 amplitude in response to the patients' own name as compared to unfamiliar names in 3 out 5 patients diagnosed as being in a VS. Such a response was also found in unconscious state such as sleep (Perrin et al., 1999). These studies hence assessed automatic rather than conscious cognitive processing. A previous study of Davis et al. (2007) showed that speech comprehension is already altered during light anesthesia suggesting that it is linked to consciousness. Using this paradigm, Coleman et al. (2009) showed that some VS patients demonstrated speech comprehension. However, these fMRI findings were strongly correlated with the patient's recovery, 6 months after the scan, suggesting that residual cognitive processing were potentially present at the time of the scan and that speech comprehension could be an indicator of consciousness re-appearance. This result has nevertheless to be replicated in the future (Coleman et al., 2009).

None of these studies investigated high-order/ controlled cognitive processing. Cognitive control implies consciousness as the participant has to understand the instruction and actively/voluntarily responds to this one. The use of "active tasks" seems therefore useful to detect conscious brain activity in severely brain injured patients. In 2006, Owen et al. developed an active task and reported the case of a young woman considered as being clinically in a VS while she showed a brain activity indistinguishable to what is observed in healthy subjects when she was asked to perform a mental imagery task (Owen et al., 2006). Recently, an active electrophysiological (ERPs) paradigm was also proposed. In this version, the subject was instructed to voluntarily direct his attention and count a target stimulus. A larger P3 response (which is often linked to cognitive functioning such as working memory; Kok, 2001) was observed when MCS patients and controls were asked to count a target compared to a passive listening condition (Schnakers et al., 2008). This response was obtained in patients showing solely a visual fixation and/or pursuit (Schnakers et al., 2008) as well as in patients presenting severe motor dysfunctions (Schnakers et al., 2009b). These results suggest a relative preservation of high-order cognitive functioning and, more exactly, of controlled attention and/or working memory in severely brain-injured patients. However, as regards the multi-determined aspect of the tasks, cognitive processes involved cannot be precisely determined. Studies using more selective and sensitive paradigms are therefore needed to better understand remnant cognitive functioning in patients recovering from coma. Additionally, even if "active" paradigms are interesting as these do not request motor or verbal responses which are often impaired in these patients, a response is obtained in a minority of patients behaviorally considered as MCS (Monti et al., 2010b; Bardin et al., 2011) stressing the importance of simplifying paradigms as well as to use multi-modal techniques to increase chances to observe conscious cognition.

Behavioural scales would have to be used in parallel to electrophysiological and neuroimaging techniques in order to better characterize the relationship between motor responses and cognition in these patients. Existing scales nevertheless mainly include multi-determined items. For example, the CRS-R which is currently considered as the most sensitive diagnostic scale assesses behaviors involving various cognitive functions without making the distinction between these (e.g., the object recognition item simultaneously requires selective attention, shifting and semantic memory). Until now, few tools assessing specific cognitive components have been developed. Usual neuropsychological tests use motor and verbal responses and cannot be used as regards typical patient's deficits (e.g., tracheostomy and severe spasticity). These tests have therefore to be adapted to this population. Previous studies have shown it is not impossible to create such tools. Whyte et al. (1995) have designed a test to detect neglect in MCS patients. This test is mainly based on visual fixation as the patient has to explore two cards presented in front of his/her right and left visual field. A preference for the cards presented on his/her right side would give information on the presence of neglect. This task illustrates the feasibility of assessing basically remnant cognitive functioning of severely brain injured patients using behavioral tools. Such testing will have to be developed further in the future.

Conclusion

Assessing residual cognition in patients with disorders of consciousness is a real challenge. Usually bedside assessment is used to detect oriented/voluntary behaviors that are supposed to reflect conscious brain activity. Misdiagnosis is however frequent. The development of sensitive and valid behavioral as well as paramedical (i.e., electrophysiological and neuroimaging) tools is particularly needed. This would allow to better investigate and characterize cognitive processing linked to consciousness in severely brain injured patients.

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