Review

Moving into the wide clinical spectrum of consciousness disorders: Pearls, perils and pitfalls

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A B S T R A C T

The last few years have been characterized by a growing interest of the medical and scientific world for the field of consciousness and its related disorders. Medically speaking, consciousness can be defined as the state of awareness of self and environment and the alertness to external stimulation, besides responsiveness to inner need.

Transient loss of consciousness can be due to alterations in cerebral blood flow leading to fainting or syncope, migraine, metabolic dysfunctions, unexpected intracranial pressure increases, epileptic seizures, and sleep disorders. Chronic disorders of consciousness are a tragic success of high-technology treatment, in an attempt to maintain or reestablish brain function, which is to be considered as the main goal of therapeutic management. Vegetative or a minimally conscious state individuals involves charitably getting the right diagnosis with an evidence-based prognosis, also taking into account the medical, ethical, and legal key factors of the ideal treatment. This paper is aimed at exploring the wide spectrum of consciousness disorders and their clinical differential diagnosis, with particular regards to those with a negative impact on patient and their caregiver quality of life, including epilepsy, sleep disorders, and vegetative/minimally conscious state.

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1. Introduction

The terms consciousness, confusion, stupor, unconsciousness, and coma have been given many different meanings so that it is really difficult to avoid ambiguity in their use. Medically speaking, consciousness can be defined as the state of awareness of self and environment and the alertness to external stimulation, besides responsiveness to inner need [1]. Advances in neurobiology of consciousness lead to believe that the upper brainstem nuclei have a pivotal role in arousal, and that the activity of the thalamus and cortex provides much of the content of consciousness [2,3].

In particular, consciousness has 2 clinical elements:

1. **Wakefulness**, which is mediated by the ascending reticular activating system (ARAS) of the brainstem and its thalamocortical connections, and
2. **Awareness** of one’s self and the environment, which is mediated by the cerebral cortex and its intracortical, thalamocortical, and cortico-sub-cortical connections [4].

Alterations one or both of these components may lead to disordered state of consciousness [5]. Disordered states of consciousness define a broad category encompassing a spectrum of cognitive abnormalities, i.e. from mild confusional states, delirium and dementia to coma, vegetative state (VS), minimally conscious state (MCS), and brain death (Figure).

2. Episodic impairment of consciousness

Transient loss of consciousness can be due to alterations in cerebral blood flow leading to fainting or syncope, migraine, metabolic dysfunctions, unexpected intracranial pressure increases, cerebral ischemia or hemorrhage, epileptic seizures, and sleep disorders [6]. Differentiating anxiety attacks, psychogenic non-epileptic seizures (PNES), and malingering from the abovementioned conditions may be really difficult.

Notably, the right diagnosis may not be reached without accurate laboratory tests and long follow-up periods.

2.1. Syncope

Syncope may be caused by a reduced cardiac output owing to heart arrhythmias, outflow obstacle, orthostatic hypotension, hypovolemia or reduced venous return. Metabolic dysfunction, caused by hypoxia, anemia, hypoglycemia or drugs, may usually lead to presyncope (i.e. a sensation of an imminent faint) or, less commonly, to syncope. Of note, consciousness may be impaired in absence seizures, generalized tonic-clonic seizures (GTCS), and complex partial seizures that, in most cases, can be easily distinguished from syncope.

However, the differential diagnosis may be very difficult when syncope is associated to myoclonic jerks, upward version of the eyes and short automatism [7–11].

2.2. Epileptic seizures

Epileptic seizures (ES) are the manifestation of cortical neuron abnormal hypersynchronization with a consequent hyperexcitable discharges. Physiologically, ES has been defined as an abrupt alteration of brain function, subsequent to a paroxysmal high-frequency and high voltage electrical discharge, mainly arising from an assemblage of excitable neurons in any part of the cerebral cortex [12,13]. It is noteworthy that seizures are frequent, aspecific expressions of neurologic disorders, including brain injury, since the leading function of the brain is the transmission of electrical impulses.

Epilepsy is defined as a brain disease characterized by a durable tendency to produce epileptic seizures with the consequent neurobiological, neuropsychological, and psychosocial complications. The diagnosis of epilepsy usually requires the existence of at least 2 unprovoked seizures 24 h apart [14]. Seizures are divided into two categories: partial seizures and generalized seizures. Partial seizures result from a neural discharge within a specific brain area, with focal symptoms that may progress (with or without consciousness impairment) to secondarily generalized seizure, resulting in tonic-clonic activity [15].

Primary generalized seizures are thought to be generated in the thalamus and other related subcortical areas, although EEG recording usually shows a simultaneous activation of both the cerebral hemispheres. Thus, they present with bilateral symptoms and/or signs, and are constantly associated to loss of consciousness. Tonic seizure is the rigid (usually brief) contracture of muscles, whereas the clonic seizure is the longer rhythmic shaking; the consequent GTCS, also defined “a grand mal”, may be considered one of the most dramatic medical illnesses. Patients affected by GTCS and idiopathic generalized epilepsy usually do not have any evidence of history, general or neurologic, laboratory or neuroimaging examination abnormalities. The awake EEG performed in individuals with GTCS may be normal, although some interictal EEG patterns may be typical of specific generalized epilepsy syndromes [16]. Of note, it is sometimes difficult to distinguish ES from PNES, anxiety attacks, and malingering [17].

Status epilepticus is traditionally defined as a continuous, incessant seizure that lasts more than 30 min, or recurrent
seizures without recovering consciousness between the seizures. Nonetheless, the treatment of such medical emergency is usually started after no more than 5 min, since there is growing evidence that after 5 min of hypoxia neurons may be irreversibly damaged [18].

2.3. Psychogenic non-epileptic seizures

Psychogenic non-epileptic seizures are commonly defined as paroxysmal episodes resembling an epileptic seizure, often leading to misdiagnosis.

 Nonetheless, PNES are considered to be psychogenic in origin, with a 20%-30% prevalence in patients attending tertiary epilepsy centers. Patients with PNES may present with a higher prevalence of post traumatic experiences with depressive mood and anxiety, fibromyalgia and chronic pain. Their medical and personal history is almost always different from patients suffering from epilepsy: the paroxysmal behaviors are mainly motor bilateral phenomena, including jerking or shaking, without objective signs of loss of consciousness; appear during the day and rarely at nighttime; the frequency does not diminish with the use of anticonvulsants, but with the use of antidepressants; during the seizure, EEG (if performed) is usually normal.

3. Sleep as a model for altered states of consciousness

Human and primate sleep is subdivided into NREM and REM sleep. During NREM sleep there is a progressive slowing of brain metabolic activity and flow from wakefulness, which is most evident in the dorsolateral prefrontal cortex (DLPC), responsible for the executive functions. Serotonin and noradrenaline neurotransmission slow down, while histaminergic and gabaaergic modulation take over. Motor activity is disfacilitated occurring only on sleep stage transitions, whilst mental activity becomes perseverative and akin to rumination; perception of external stimuli is dull or absent.

 Instead, during REM sleep, cholinergic firing from the latero-dorsal tegmentum (LDT) and the peduncolo-pontine nucleus (PPN), stimulate the occipital cortex inducing vivid visual imagery, which is internally generated owing to complete shut-off of output-input gating. Movement is not only disfacilitated as in NREM sleep, but actually actively inhibited at the level of spinal motor neurons through the sublateral dorsal nucleus (SLD) stimulation. Moreover, REM sleep carries a cumulative excitation level similar to that observed during the waking state, with the exception of the fronto-parietal cortices, which still maintain the low level of activity of slow wave sleep (SWS) [19].

 Notably, wake, NREM and REM sleep are not to be seen as discreet all-or-nothing states of being, but rather their intrinsic components may rapidly oscillate and recombine in hybrid states of pathological (sleep disorders) or simply unusual (parasomnias) consciousness misfits [20].

 Some clinical examples of dissociated states of consciousness mediated from sleep pathology include narcolepsy, disorders of arousal (DOA) and REM behavior disorders.

3.1. Narcolepsy

It is a rare neurological sleep disorder characterized by a tetrad of symptoms: excessive daytime sleepiness (EDS) with irresistible nap urgency, cataplexy, hypnagogic/hypnopompic hallucinations and paralysis [21].

The lack of hypothalamic orexin/hypocretin in this disease is responsible for both sleepiness and incorrect coupling of sleep markers across sleep-wake phases [22]. An exaggerated REM propensity explains the persistence of REM sleep markers at the sleep-wake transition (hypnagogic hallucinations and paralysis) or during wakefulness through the inhibition of muscle tone, prompted by strong emotions, during cataplectic attacks.

Sleep onset REM periods (SOREMPs), both at night and during daytime naps, are the distinctive physiological markers of the disease, even if in specific conditions, such as severe sleep deprivation by drugs, environmental or clinical conditions, SOREMPs may be found less frequently and consistently than in narcolepsy [23,24].

3.2. Disorders of arousal

Disorders of arousal (DOA) are NREM parasomnias, undesirable, unusual phenomena occurring as behavioral, autonomic or experiential events. They occur out of deep stages of NREM, typically during SWS in the first third of the night [25]. They are partially due to an intrinsic predisposition toward arousal instability, tend to recur as a familial trait, precipitated by sleep deprivation alone or due to other sleep disorders responsible for sleep instability [26,27]. DOA include sleep walking, night terrors and confusional arousals, which are altered states of consciousness to be distinguished from other paroxysmal events, including seizures from temporal or frontal nocturnal epilepsy, with which they share local patterns of brain activation at night.

Sleep walking is characterized by complete or abortive walking behavior occurring unexpectedly at night out of SWS, prompted by an incomplete spontaneous arousal. At the end of the episode the patient spontaneously resumes nocturnal sleep in bed or elsewhere and does not recall his behavior in the morning or even immediately when awakened. Functional neuroimaging (SPECT) of the sleep walking episode demonstrates activation of thalamo-cingulate pathways, paralleled by reduced local cerebral blood flow in the fronto-parietal cortices, as if the brain were motorically activated but unconscious due to the switch-off of the executive functions [28]. Exactly the same areas are at stake during paroxysmal arousals of nocturnal frontal lobe epilepsy (NFLE) [29]. A similar EEG/brain activity dissociation supports confusional arousals both in children and, more rarely, in adults in the form of sleep inertia or sleep drunkenness [30]. Basic drives may complicate these episodes with the occurrence of sleep-related eating disorder (SRED) or complex auto or hetero sex behaviors (sexsomnia) [31], which are performed by the subject while still partially asleep and in an altered state of consciousness, which is not morally and legally prosecutable [32].

During night terrors there is, instead, an intense autonomic activation including mydriasis, diaphoresis, tachycardia and tachypnea. Screaming, vocalization or inconsolable crying usually alert parents or bed partners. Any attempt to stop or
console the patient is unsuccessful and may actually only prolong the episode, which as a rule, will be forgotten in the morning by the unaware child. Night terrors are very rare in adults (2.7%) and usually represent reemergence of childhood behaviors, whereas sleepwalking has a higher life time (22.4%) but lower adult prevalence (1.7%) [33].

3.3. REM behavior disorder (RBD)

REM behavior disorder (RBD) is an interesting reverse example of motor activation during REM sleep, taking place instead of the physiological state trait of motor inhibition. Therefore dreams, especially violent dreams, may become “enacted” due to the impairment of the physiologic REM related inhibition of muscle tone, thereby causing self or hetero injurious behaviors during sleep [34]. Acute forms of the disease may be iatrogenic due to intoxication or withdrawal from substances/medications such as alcohol, barbiturates or antidepressants.

Alteration of the brainstem motor networks responsible for motor inhibition (SLD, periculocoeeruleus and/or long descending fibers from the forebrain), are the anatomical basis of RBD. Video-polygraphic recordings allow instrumental confirmation of the clinical diagnosis via detection of REM sleep without atonia.

The extreme form of RBD+ condition is status dissociatus (SD), a clinical condition of extreme continuous state dissociation where dream-like and delirious agitated behaviors occur during apparent sleep, albeit no conventional sleep stages may be classified due to complete loss of any kind of physiologic state markers [35].

Sleep itself and sleep disorders may indeed teach us a lot about altered states of consciousness and may be useful to better understand conditions typical of psychiatric and comatose patients.

4. Acute consciousness disorders

4.1. Confusion

The term confusion lacks precision, but in general it denotes an inability to think with customary speed, clarity, and coherence. All states of confusion are marked by some degree of inattentiveness and disorientation, bewildernent, and difficulty following commands. In this condition the patient does not take into account all elements of his/her immediate environment, with a degree of imperceptiveness and distractibility, referred to traditionally as “clouding of the sensorium”. Confusion results most often from a process that influences the brain globally, such as a toxic or metabolic disturbance or a dementia. However, a confusional state can also accompany focal cerebral disease in various locations, particularly in the right hemisphere, or result from disorders that may disturb mainly language, memory, or visuo-spatial orientation, but these are readily distinguished from the global confusional state [36].

4.2. Delirium

In some medical writings, particularly in the psychiatric literature, the terms delirium and confusion are used interchangeably, the former connoting nothing more than a characterless confusional state in which hyperactivity may be prominent. On the contrary, the vivid hallucinations, the inaccessibility of the patient to events other than those to which he is reacting at the moment, the extreme agitation, the tendency to tremble, startle easily and the convulse, and the signs of over activity of the autonomic nervous system, as well as a normal EEG tracing, suggest the presence of the “syndrome of delirium tremens” (observed most often but not exclusively in alcoholics) [36]. It is generally claimed that organic lesions of the frontal lobes can easily cause delirium [37].

4.3. Drowsiness and stupor

In these states, mental, speech, and physical activity are reduced. Drowsiness denotes an inability to sustain a wakeful state without the application of external stimuli, and it is characterized by decreased respiratory and heart rate [38] lower body temperature [39] and increased threshold of response to external stimuli [40]. This state is indistinguishable from light sleep, with slow arousal elicited by speaking to the patient or applying a tactile stimulus [41].

Stupor describes a state in which the patient can be roused only by vigorous and repeated stimuli, when he opens his eyes, looks at the examiner, and does not appear to be unconscious; response to spoken commands is either absent or slow and inadequate; restless or stereotyped motor activity is common in stuporous patients and there is a reduction in the natural shifting of positions. When left unstimulated, these patients quickly drift back into a sleep-like state [42].

4.4. Coma

The most common disorder of consciousness that immediately follows severe brain injury is coma, a time-limited state characterized by eyes-closed unresponsiveness, in the absence of a sleep-wake cycle [42,43]. Comatose patients fail to respond to even the most vigorous stimulation, and when given noxious stimulation, patients may not move at all or may display stereotyped/reflexive movements only.

Coma is always a symptomatic expression of an underlying disease, being brain lesions (cortical, brainstem or white matter damage), metabolic or nutritional disorders, poisoning, infections of the CNS, hypo- or hyperthermia and trauma the most common causes [44]. All of the aforementioned causes have the common feature of interfering with the ARAS and its several projections to the cerebral cortex [45] and the state of coma is the result of damage to this system [44].

As a general rule, recovery from coma of metabolic and toxic causes is better than anoxic coma, with head injury occupying an intermediate prognostic position. Most coma-tose patients following severe stroke have high probability to die, being subarachnoid hemorrhage an exception, as it may induce coma also in absence of hydrocephalus [42]. Post-anoxic coma is an unconsciousness state secondary to global cerebral anoxia, mainly following a cardiac arrest. Post-anoxic coma that lasts more than several hours has normally a bad outcome [46]. Indeed, consciousness recovery arises in over 20%–30% of the patients remaining in coma for at least 24 h. To
this end, research is aimed at investigating the potential elements that may reliably predict bad outcomes in post-anoxic subjects. Indeed, the PRO PAC study [46] has found that the bilateral absence of the early cortical response after median nerve somatosensory potentials should be considered one of the most consistent predictor of bad outcome.

Notably, in the late 1950s European neurologists paid attention to a state of coma in which the brain was irreversibly damaged and had ceased to function, but pulmonary and cardiac function could still be maintained by artificial means. Mollaret and Goulon referred to this condition as “coma depasse” (namely, brain death) [47], with the diagnosis based on the: (i) absence of cerebral functions; (ii) absence of brainstem functions; (iii) irreversibility of the state.

5. Chronic unconsciousness

Chronic disorders of consciousness are a tragic success of high-technology treatment, in an attempt to maintain or reestablish brain function, which is to be considered as the main goal of therapeutics. Management of vegetative or a minimally conscious state individuals involves charily getting the right diagnosis with an evidence-based prognosis, also taking into account the medical, ethical, and legal key factors of the ideal treatment [48].

The VS and MCS are disorders of consciousness (DOC), which may be acute and reversible, or chronic and irreversible (Table), and are usually due to diffuse lesions of the thalamus or the frontal-temporal-parietal cortices and their white-matter interconnecting tracts [49].

5.1. Vegetative state

Vegetative state, recently named unawareness unwakefulness syndrome (UWS) by The European Task Force on Disorders of Consciousness [50], is a behaviorally defined disorder, whereby patients do not have either any evidence of self or environmental awareness or any voluntary motor responsiveness in the presence of eye-open wakefulness; such condition may be either transitory (leading to a MCS) or irreversible. As in coma state, patients can have spontaneous or stimulus-induced, stereotyped movements, and may retain brainstem regulation of visceral autonomic function that would suggest that the lower brainstem is undamaged [51].

However, the main behaviorally difference from coma is that VS patient present with a nearly normal alternation of eyes-open and eyes closed periods. Nonetheless, this does not imply that VS patients have normal sleep-wake cycles, since their EEGs display a monotonous slow pattern regardless of whether the eyes are open or closed, or they only have fragmented components of normal electrographic sleep-wake phenomenology. Indeed, the eye opening periods reflect only a rudimentary arousal pattern that involves upper brainstem nuclei.

Interestingly, where VS evoked cortical activity can be recorded, it is fragmented and not integrated to the various networks linked to the state of consciousness. Recovery of consciousness may be partly related to a reversal of such silent long-range cortical connections [52,53].

Different studies have investigated the response to auditory and painful somato-sensory stimuli, leading to interesting findings. Indeed, it has been shown that, although the primary auditory cortices are activated by auditory stimuli, higher order multi-sensory association areas are not [54]. In this condition, patients have a functional disconnection between the primary auditory, multi-modal associative and limbic areas. Moreover, the administration of painful stimuli in VS patients has been demonstrated to activate only the primary somato-sensory cortex, with a functional disconnection from higher order associative areas, including the so-called “pain matrix” [55,56].

VS may represent a transitional state on the way to recovery of consciousness or could be a chronic condition in cases of more severe brain injuries. Persistent vegetative state is a term used for patients who have remained in VS for an arbitrarily defined duration of 30 days, whereas permanent vegetative state [57] is applied to patients in VS after global ischemia for 3 months or TBI for 1 year. However, such terms are not recommended and they should be replaced by the injury etiology (traumatic versus non-traumatic) and the duration of the condition, since these key elements seem to affect outcome [58].

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5.2. Minimally conscious state

Minimally conscious state (MCS) is the next level of recovery on the continuum from VS to full consciousness, defined as a state of severely impaired consciousness, where patients present with marginal but explicit behaviors, thus demonstrating some evidence of self or environmental awareness.

MCS includes a more heterogeneous group of patients than VS, because the definition allows for a wide range of behaviors, whereas VS only includes reflexive movements. In MCS, “low-end behaviors” include visual tracking to a mirror, localization of noxious touch, and inaccurate verbalization, whereas “high-end” behaviors include consistent movement to command and choosing correctly between 2 objects [58]. Patients with only low-end behaviors can be difficult to differentiate from VS, because such behaviors may be slight and infrequent. This differentiation may be important because patients in MCS have significantly better prognoses for recovery than those in VS [59]. The EEG pattern shows in both conditions a diffuse slowing of brain electrical activity, but often with a generalized polymorphic delta or theta rhythm in the VS [60]; however, EEG is not of great help in their differential diagnosis. Based on growing clinical and scientific evidence, a major issue is to evaluate and understand the presence of cortical activation in patients with clinical diagnosis of VS, documented by both event-related potentials (ERPs), and fMRI [61,62]. To this end, some authors [63] have proposed to identify an additional intermediate category between VS and MCS under the name of “non-behavioral MCS”, others more carefully define patients with “islands” of cognitive activity [64]. These patients cannot exhibit any behavioral evidence of cognition due to severe motor impairment, although they are minimally conscious.

The distinction between coma, brain death, VS and MCS (although critical) is moderately robust in clinical practice, but it is not immune from practical and theoretical mistakes. On a practical level, there are evident examples that VS is often misdiagnosed in patients who are indeed aware of themselves and of their environment [65,66].

MCS has to be cautiously examined to be distinguished from those with locked-in syndrome (LIS), since both the conditions are characterized by minimal behavioral interaction with the environment [67]. In particular, LIS is a disorder where the patient is aware and awake, although is not able to move or verbally communicate, owing to a nearly complete paralysis of all voluntary muscles, with the exception of the eyes. Locked-in patients have higher levels of metabolic activity in some regions of the medial parietal cortex than VS or MCS patients [53]. In addition, there is no evidence of cortical function reduction in such patients, suggesting that LIS is a condition of motor deafferentation in which consciousness and intellectual capacity are perfectly preserved [44]. Notably, emerging neuroimaging and neurophysiological data are demonstrating a new diagnostic category, namely “functional locked-in syndrome”, to emphasize the dissociation between the extreme behavioral motor dysfunctions and the partially preserved cognitive functions [56,68–74].

To date, the best-standardized and most frequently used tool for the clinical assessment of chronic disorders of consciousness, mostly to distinguish VS from MSC, is represented by the Coma Recovery Scale-Revised (CRS-R) [75].

The scale was first described in 1991 [76] and revised in 2004 [75], and it consists of six sub-scale addressing auditory, visual, motor, oro-motor/verbal, communication and arousal processes. The lowest score on each sub-scale describes reflexive activity, while the highest score represents purposeful behaviors. Moreover, according to the different scores obtained, MCS can be divided into: MCS – describing “low-level behavioral” responses (i.e. visual pursuit, localization of noxious stimulation or feasible behavior), and MCS- with “high-level behavioral responses” (including, command following, comprehensible verbalizations and non-functional communication) [68].

6. Conclusions

Disordered states of consciousness define a broad category encompassing a spectrum of cognitive dysfunction, whose differential diagnosis is still challenging, especially concerning the chronic state. To date, bedside clinical examination represents the gold standard for establishing diagnosis of DOC. Although neuroimaging and electrophysiology techniques play a major role in the identification of the sites of lesional damage, they have to be considered as auxiliary in the diagnostic process. Based on cognitive and motor skills of the patient, it is possible to show up a continuum from coma state to full recovery of consciousness. The transition from coma to VS is discernible by the opening of the eyes; the conversion from VS to the MCS is characterized by voluntary intentional behavior, whilst the step from MCS to severe disability by the presence of purposeful communication. However, the evaluation of these patients is extremely difficult, and depends on subjective interpretations of the patient’s behavior, either spontaneously or in response to any stimuli. This difficulty unfortunately may lead to frequent diagnostic errors and confusion, with high rates of misdiagnosis [77]. For this reason, a profound knowledge of the clinical manifestation of DOC conditions, a wider use of standardized behavioral scales, besides the development of new diagnostic tools, should be fostered in the future in order to reduce diagnostic errors.

Conflict of interest

The authors state no conflict of interests.

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Global functional connectivity reveals highly significant differences between the vegetative and the minimally conscious state. J Neurol 2013;260:975–83.


