Cerebral Function in Coma, Vegetative State, Minimally Conscious State, Locked-in Syndrome, and Brain Death

S. Laureys, J. Berré, and S. Goldman

Introduction

Progress in intensive care has increased the number of patients who survive severe acute brain injury. The majority of these patients recover from their coma within the first days after the insult, others will take more time and go through different stages before fully or partially recovering awareness (e.g., minimally conscious state, vegetative state) or will permanently lose all brain functions (i.e., brain death). One of the most challenging problems facing intensivists is understanding the natural history of severely brain injured patients and their possibility of recovery. Clinical practice shows how delicate it is to infallibly recognize unambiguous signs of conscious perception of the environment and of the self in these patients. This complication is reflected in the frequent misdiagnosing of the locked-in syndrome, minimally conscious state and vegetative state [1, 2]. First, objective assessment of residual brain function in severely brain injured patients is difficult because motor responses may be small or inconsistent. This is even more so because consciousness is not an all-or-none phenomenon but part of a continuum [3]. Second, there is a theoretical limitation to the certainty of our clinical diagnosis, since we can only infer the presence or absence of conscious experience in another person [4]. In the present paper, we will first try to define consciousness as it can be assessed at the patient's bedside. We then review the major clinical entities of altered states of consciousness encountered in the intensive care unit. Finally, we discuss the functional neuroanatomy of these conditions as assessed by positron emission tomography (PET) scanning.

Consciousness, awareness and arousal

There is at present no satisfactory, universally accepted definition of human consciousness. The word consciousness originates from the Latin *conscio*, formed by the coalescence of *cum* (with) and *scio* (to know). The Latin root was used to refer to knowledge shared with another [5]. William James defined consciousness as awareness of oneself and the environment [6]. The interpretation of this delineation depends however on the neuroscientific or philosophical approach of the authors. For clinical purposes, consciousness consists of two basic elements: *arousal* and *awareness* [7].

Arousal refers to the behavioral continuum that occurs between sleep and wakefulness. This is not an on-off mechanism as it can show rapid fluctuations in response to external stimulation (intense, unexpected or novel stimuli) called

orienting reaction or vigilance. At the patient's bedside, arousal is defined as the presence of prolonged periods of spontaneous opening of the eyes.

Awareness refers to the collective thoughts and feelings of an individual. Clinically, however, our operational definition is limited to the appraisal of the potential to perceive the external world and to voluntary interact with it (also called *perceptual awareness*). In practice this is done by careful and repeated examination of the capacity to formulate reproducible, voluntary, purposeful and sustained behavioral responses to auditory, tactile, visual, or noxious stimuli.

Self-consciousness (also called self-awareness) can refer to awareness of stimuli that impinge directly on our person (e.g., being aware of the seat you sit on) or it can refer to the control of "an idea of oneself " (e.g., recognizing yourself in the mirror). The latter can be done from the age of 18 months - as by chimpanzees but not by macaque or rhesus monkeys [8]. "Awareness of awareness" (e.g., the knowledge of yourself as a person in a social and cultural world) is thought to emerge around 5 years of age [5].

Clinical definitions

Coma

Coma is characterized by the absence of arousal and thus also of consciousness. It is a state of unarousable unresponsiveness in which the patient lies with the eyes closed and has no awareness of self and surroundings. Although there are gradations in the depth of coma, the patient lacks the arousal cycles of sleep-wakefulness characteristic of vegetative state (Table 1). The behavioral repertoire of coma consists entirely of reflex activity and indicates failure of both the reticular activating system and the cortex [7]. To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness, coma must persist for at least an hour. In general, comatose patients who survive begin to awaken and recover gradually within 2 to 4 weeks or enter a vegetative or minimally conscious state.

Vegetative State

Patients in a vegetative state are awake but unaware of self and environment [9]. Jennet and Plum cited the Oxford English Dictionary to clarify their choice of the term "vegetative": to vegetate is to "live a merely physical life devoid of intellectual activity or social intercourse" and vegetative describes "an organic body capable of growth and development but devoid of sensation and thought".

"*Persistent* vegetative state" is arbitrarily coined as a vegetative state present one month after acute traumatic or nontraumatic brain injury [10] but does not imply irreversibility. "*Permanent* vegetative state" denotes irreversibility after three months following a nontraumatic brain injury and 12 months after traumatic injury. However, even after these long and arbitrary delays, some patients may exceptionally recover.

Table 1. Characteristics of comatose, vegetative, minimally conscious, locked-in and brain-death patients

Condition	Arousal	Awareness	Motor function	Respiratory function	EEG	FDG-PET	Prognosis
Coma	Absent	Absent	No voluntary movement	Depressed, variable	Major generalized slowing	40 to 50 % decrease	Recovery, vegetative state or death within 2 to 4 weeks
Vegetative state	Normal	Absent	No voluntary movement	Normal	Major generalized slowing	50 to 60 % decrease (associative cortex is most impaired)	Depends on etiology (traumatic, non-traumatic)
Minimally conscious state	Normal	Minimally present	Minimal but reproducible voluntary movement	Normal	Non-specific generalized slowing	20 to 40 % decrease (?) (precuneus is relatively spared)	Unknown, better than vegetative state
Locked-in syndrome	Normal	Normal	Complete paralysis except for eye movements	Normal	(Near) normal	Normal or near normal activity	Persistent quadriplegia with prolonged survival
Brain death	Absent	Absent	Spinal reflexes	Absent	Isoelectric	No activity in brain and brainstem	Irreversible

Note: These characteristics will not apply to every patient

EEG: electroencephalogram; *FDG-PET:* [^{18}F]fluorodeoxyglucose-positron emission tomography

Patients in a vegetative state usually show reflex or spontaneous eye opening and breathing. At times they seem to be awake with their eyes open, sometimes showing spontaneous roving eye movements and occasionally moving trunk or limbs in meaningless ways; at other times their eyes are shut and they appear to be asleep. They may be aroused by painful or prominent stimuli opening their eyes if they are closed, quickening their breathing, increasing heart rate and blood pressure and occasionally grimacing or moving. Pupillary, corneal, oculocephalic and gag reflexes are often preserved. They can make a range of spontaneous movements including chewing, teeth-grinding and swallowing. More distressingly, they can show rage, cry, grunt, moan, scream or smile reactions spontaneously or to non-verbal sounds. Their head and eyes sometimes, inconsistently, turn fleetingly towards new sounds or sights. These abilities are also seen in another group of patients showing preserved wakefulness without awareness - namely, infants with anencephaly - and are considered to be of subcortical origin.

The diagnosis of vegetative state should be questioned when there is any degree of sustained visual pursuit, consistent and reproducible visual fixation, or response to threatening gestures. When patients undergo a transition from the vegetative state to a state if awareness, one of the first and most readily observed clinical signs of this transition is the appearance of sustained visual pursuit. [10]. The crucial thing one has to ascertain is the formal absence of any sign of conscious perception or deliberate action. Any evidence of communication, including a consistent response to command, or any purposeful movement rule out the diagnosis. This evidence can easily be missed, especially in patients whose senses and motor capacities are severely impaired and in whom a blink of an eye (e.g., locked-in syndrome) or the subtle movement of a finger may provide the only evidence of awareness. Careful and prolonged observation is indispensable as fluctuating arousal or motivation can prevent the assessment of minimal yet present awareness in these patients.

Apallic state or syndrome is an archaic term for a condition that is now considered equivalent to vegetative state. The term *neocortical death* has been used differently by various authors. Some refer to it as a vegetative state with absence or substantial slowing of electrocortical activity on electroencephalography (EEG), in addition to the characteristics of vegetative state. Others equate neocortical death with the ostensible death of all neurons of the cerebral cortex. It is not clear whether this term denotes a clinical syndrome or its electrical, pathologic, or anatomical features [10]. The American Neurological Association has suggested to abandon the terms apallic state or syndrome, neocortical death, coma vigil, alpha coma and permanent unconsciousness [11].

Minimally Conscious State

"Minimally conscious state" replaces the term "minimally responsive state" which was first defined by the American Congress of Rehabilitation Medicine in 1995. It is used to describe patients who are unable to follow instructions reliably or communicate, but who demonstrate inconsistent but reproducible behavioral evidence of awareness of the environment or self-awareness [12]. Patients in minimally conscious state can

show reproducible visual fixation and emotional or motor behavior that are contingent upon the presence of specific eliciting stimuli such as episodes of crying that are precipitated by family voices only, command following, object manipulation, intelligible verbalization and gestural or verbal yes/no responses. Outcome is thought to be better relative to vegetative state [13].

Akinetic mutism is a rare condition that has been described as a subcategory of the minimally conscious syndrome [12], while other authors suggest that the term should be avoided [11]. It was first introduced by Cairns in 1941 to describe a condition characterized by severe poverty of movement, speech and thought without associated arousal disorder or descending motor tract impairment [14]. Typical for akinetic mutism is the complete or near-complete loss of spontaneity and initiation, such that action, ideation, speech and emotion are uniformly reduced. The absence of internally guided behavior allows attention to be passively drawn to any environmental stimulus that the patient is exposed to [13].

Locked-in Syndrome

The term "locked-in" syndrome was introduced by Plum and Posner in 1966 to reflect the quadriplegia and anarthria brought about by the disruption of corticospinal and corticobulbar pathways, respectively [7]. In marked contrast with the previously described conditions, the defining feature of the locked-in syndrome is the relative preservation of cognition. The locked-in syndrome superficially resembles vegetative state, minimally conscious state and akinetic mutism in that wakefulness is generally well preserved but there is little or no evidence of purposeful verbal or motor behavior [15]. Consciousness, vertical eye movement and eyelid blinking are intact because the pontine tegmentum is spared and provides a mechanism for recognizable command following and communication responses. The locked-in syndrome can also be associated with diseases of peripheral motor nerves or paralysis produced by the administration of neuromuscular blocking agents. The mortality rate has been estimated at 60%, with respiratory failure cited as most frequent cause of death [16].

Brain Death

The concept of brain death as defining the death of the individual is largely accepted. Most countries have published recommendations for the diagnosis of brain death as a necessary prerequisite for organ donation, but the diagnostic criteria of brain death differ from country to country [17]. Some rely on the death of the brainstem only [18], others feel that death of the whole brain including the brain stem is mandatory [17]. However, the clinical criteria for brain death are very uniform and based on the loss of all brainstem reflexes and the demonstration of apnea in an irreversibly comatose patient [19]. The various brain death codes mainly differ for using technical confirmatory tests to corroborate these clinical signs. Most guidelines allow the use of EEG, which must demonstrate electrocortical silence. Other neurophysiological tests which are accepted in some countries as a confirmatory test are: cerebral panangiography or doppler sonography (demonstrating the cessation of brain perfusion); brain scintigraphy (confirming the loss of isotope uptake into the brain)

and evoked potentials (demonstrating the successive loss of activity of various afferent pathways).

Functional neuroanatomy

Coma

Coma can result from diffuse bihemispheric cortical or white matter damage secondary to neuronal or axonal injury, or from focal brainstem lesions that disrupt the rostral segment of the reticular activating system. [18F]fluorodeoxyglucose-PET has shown a 40 to 50 % reduction of overall gray matter metabolism in traumatic or hypoxic coma [20, unpublished data]. In patients who recovered from a postanoxic coma, cerebral metabolic rates for glucose (CMRGlu) still showed a 25 % decrease [21]. However, cerebral metabolism has recently been shown to correlate poorly with the level of consciousness, as measured by the Glasgow Coma Scale, in mild to severely head-injured patients studied within the first month following head trauma [22]. At present, there is no established correlation between CMRGlu depression and patient outcome.

A global depression of cerebral metabolism is not unique to coma. When different anesthetics are titrated to the point of unresponsiveness, the resulting reduction in CMRGlu is similar as that observed in comatose patients [23-25]. The lowest values of brain metabolism were reported during propofol anesthesia (72 %
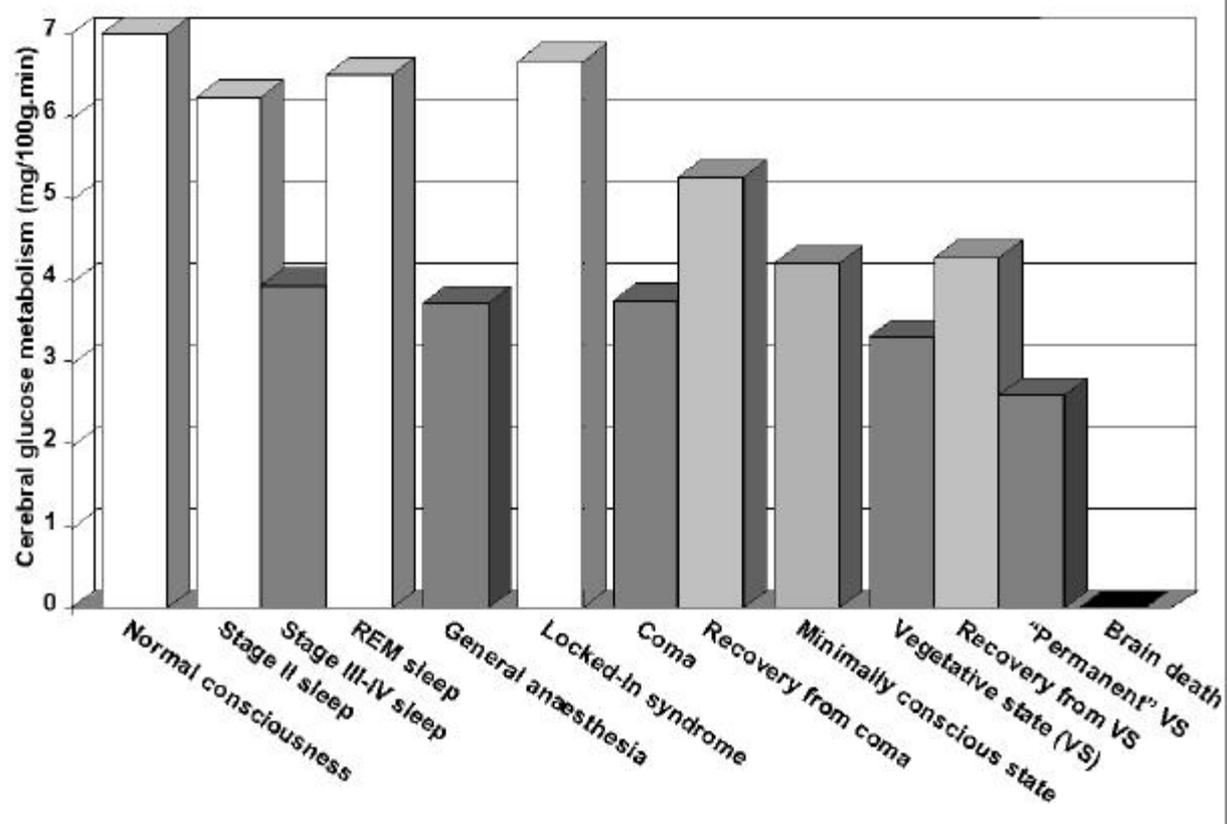

Fig. 1. Cerebral metabolism in the different diagnostic groups (for references see text)

decrease). Another example of transient metabolic depression can be observed during deep sleep (stage III and IV) [26, 27]. In this daily physiological condition CMRGlu can drop to nearly 60 % below normal values (Fig. 1).

Vegetative State

In vegetative state, the brainstem is relatively spared whereas the gray or white matter of both cerebral hemispheres is widely and severely injured. PET has shown a 50 to 60 % reduction in global cerebral metabolism of vegetative patients [20, 21, 28, 29]. In *permanent* vegetative state (i.e., 12 months after a trauma or 3 months following a nontraumatic brain injury), CMRGlu values drop to 60 to 70 % below normal [20]. This progressive loss of metabolic functioning over time is the result of progressive Wallerian and transsynaptic neuronal degeneration. Characteristic of vegetative patients is a relative sparing of CMRGlu in the brainstem (encompassing the pedunculopontine reticular formation), the hypothalamus and the basal forebrain [30]. The functional preservation of these structures allows for the preserved arousal, respiration, and other autonomic functions in these patients. The other hallmark of the vegetative state is a systematic impairment of CMRGlu in the polymodal associative cortices (bilateral prefrontal regions, Broca's area, parieto-temporal and posterior parietal areas and precuneus) [31]. These brain regions are known to be important in various consciousness-related functions such as attention, memory and language. It is still controversial whether the observed metabolic impairment in this large cortical network reflects an irreversible structural neuronal loss [32] or a functional and potentially reversible damage. However, in the rare and fortunate vegetative patients who recover awareness of self and environment, PET shows a functional recovery of metabolism in these same cortical regions [33, 34]. Moreover, we demonstrated that the resumption of long-range functional connectivity between these associative cortices and between some of these and the thalami plays an important part in the restoration of their functional integrity [35]. The cellular mechanisms which underlie this functional normalization remain putative: axonal sprouting, neurite outgrowth, cell division (known to occur predominantly in associative cortices in normal primates [36]) or even apoptosis. This residual cerebral plasticity during vegetative state has been largely overlooked and deserves further investigation. The challenge is now to identify the conditions in which and the mechanisms by which some vegetative patients may recover consciousness.

The study of possible residual cognitive processing in vegetative state has been limited to anecdotal case reports [37-40]. Our group was the first to assess auditory processing in a representative group of vegetative patients [41]. So far, changes in regional cerebral blood flow (rCBF) and functional cerebral connectivity have been prospectively studied using $H_2^{15}O$-PET in 17 patients. Auditory click stimuli still activated bilateral primary auditory cortices in vegetative patients but hierarchically higher-order multimodal association cortices failed to activate. Moreover, we have shown a cascade of functional disconnections along the auditory cortical pathways, from primary auditory areas to multimodal and limbic areas, suggesting that the observed residual cortical processing in the vegetative state

cannot lead to integrative processes thought to be necessary to attain the normal level of awareness.

Minimally Conscious State

Because criteria for the minimally conscious state were only recently introduced [12], there are very few neuropathologic or functional imaging data concerning this condition. *Akinetic mutism* is classically caused by bilateral lesions in orbito-mesial frontal cortex, limbic system encompassing septum and anterior cingulate cortex and paramedian meso-diencephalic reticular formation [42]. The global inertia is thought to be the result of inadequate cortical activation arising from disrupted reticulo-cortical and limbic-cortical circuits [7]. In our experience, minimally conscious patients show a very different pattern of brain metabolism compared to that observed in vegetative patients. The region that systematically differentiates both groups of patients is localized in the medial parietal cortex (precuneus) and adjacent posterior cingulate cortex (unpublished data). Interestingly, this area is one of the most active brain regions in conscious waking [43] and is one of the least active regions in unconscious states such as halothane [25] or propofol [44] induced general anesthesia and slow wave sleep [26]. We have previously postulated that this multimodal association cortex represents part of the neural network subserving human awareness [31].

Locked-in syndrome

Classically, structural brain imaging (magnetic resonance imaging) may show isolated lesions (bilateral infarction, hemorrhage, or tumor) of the ventral portion of the basis pontis or midbrain. It is important to stress that EEG and evoked potentials do not reliably distinguish the locked-in syndrome from the vegetative state [10]. PET scanning has shown significantly higher metabolic levels in brains of patients in the locked-in state compared to patients in the vegetative state [29]. Moreover, we have studied two cases of locked-in syndrome where there was no single voxel in the supratentorial gray matter that showed a significantly lower CMRGlu than that observed in our healthy control subjects (unpublished data). These findings emphasize the terrifying situation of an intact awareness of self and environment in sensitive beings, locked in immobile bodies.

Brain death

Functional imaging using cerebral perfusion tracers and single photon emission tomography (SPECT) [45] or cerebral metabolism tracers and PET [46, unpublished data] typically show an "empty skull" picture in brain death patients confirming the dead of the "whole brain".

Conclusion

Comatose, vegetative, minimally conscious or locked-in patients represent a problem in terms of diagnosis, prognosis, treatment and everyday management at the ICU. At

the patient's bedside, the evaluation of possible cognitive function in these patients is difficult because voluntary movements may be very small, inconsistent and easily exhausted. Functional neuroimaging cannot replace the clinical assessment of patients with altered states of consciousness. Nevertheless, it can describe objectively how deviant from normal is the cerebral activity and its regional distribution, at rest and under various conditions of stimulation. The quantification of brain activity differentiates patients who sometimes only differ by a brief and incomplete blink of an eye. In our opinion, the use of PET on a wider and wider scale and the future use of functional magnetic resonance imaging (fMRI) will substantially increase our understanding of severely brain injured patients.

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