Long-lasting coma

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Introduction

Coma is usually a transient state that occurs as a result of a severe brain injury (Young, 2009). Generally, patients in a coma either progress to full recovery of consciousness or die. A third and much less common mode of progression is the transition into unresponsive wakefulness syndrome (UWS, formerly known as the vegetative state), a condition in which patients appear to be awake, but exhibit no signs of awareness of themselves or of their environment (Royal College of Physicians, 2003; Laureys et al., 2010). Instead, the persistence of a true comatose state four weeks after cerebral damage is considered to be very rare (Monti et al., 2010). Furthermore, in the past, the term “chronic coma” was applied to patients who would have been more accurately classified as having UWS (Guérit, 1994). As a consequence, the literature contains no clinical, neurophysiological or neuroimaging descriptions of patients in a long-lasting coma (LLC). In this report, we describe the case of a patient who was still in a comatose state 14 months after his initial brain injury. We hope that this report will prompt a discussion about both the pathophysiological and the ethical issues associated with this very rare clinical condition.

Case description and neurophysiological and neuroimaging data

A 46-year-old man with a history of epilepsy had an automobile accident that resulted in brain and thoracic trauma with cardiorespiratory arrest. He received advanced life support, recovered cardiopulmonary functions approximately 30 minutes after initiation of resuscitation, and was subsequently admitted to the intensive care unit (ICU) in a comatose state [Glasgow Coma Scale (GCS) score of 3]. A computed tomography scan showed a right parietal lobe contusion, multiple facial and rib fractures, bilateral scapular fractures, and a fracture of the fourth lumbar vertebra. A brain magnetic resonance imaging (MRI) scan performed eight days after the injury revealed evidence of massive hypoxic damage associated with signs of traumatic brain injury (Fig. 1). After 41 days of hospitalization in the ICU, the patient was admitted to our Unit for Severe Acquired Brain Injuries (USABI), which specializes in the rehabilitation of patients with post-acute disorders of consciousness. Over the following thirteen months of the patient’s stay at the USABI, he underwent daily neurological examinations performed by neurologists (CB,
AS) with expertise in the evaluation of patients with disorders of consciousness. They documented the persistence of a comatose state without evidence of transition into UWS, according to the current diagnostic criteria (Royal College of Physicians, 2003). Neurological examination fourteen months after the initial brain injury showed that the patient had a GCS score of 4, with no brainstem reflexes, no respiratory drive and a persistent need for respiratory support, and increased muscular tone and deep tendon reflexes. Brain death was ruled out by the ongoing presence of extensor posturing in the upper extremities after noxious stimulus presentation (Wijdicks et al., 2010). The patient's GCS score had been 3 until the third month after the brain injury, when it advanced to 4 (E1, V1, M2), after which no further changes occurred. The patient was also evaluated weekly with the Coma Recovery Scale Revised (CRS-R) (Giacino et al., 2004), which is considered the most appropriate tool for the assessment of patients with disorders of consciousness (Seel et al., 2010). In the third month after the brain injury, the patient's CRS-R score increased from 0 (this had been his score since admission) to 1 when he exhibited abnormal posturing that changed his motor subscale score from 0 to 1. No further changes occurred thereafter. Monthly electroencephalographic (EEG) evaluations showed low amplitude (<20 μV) background activity, which was not reactive to opening of the eyes or to presentation of auditory or painful stimuli, and some epileptiform activity (Fig. 2). A 24-hour EEG recording was devoid of electrophys-
iological signs of sleep-wake cycles. An advanced quantitative EEG analysis based on operational architectonics (Fingelkurts et al., 2012a,b) will be reported in a separate article. The evaluation of mismatch negativity, an event-related potential that, in the context of repetitive auditory stimulation, is automatically generated in the brain in response to a stimulus that deviates from the preceding stimulus, revealed no responses either to frequent or to deviant stimuli. Study of median nerve somatosensory evoked potentials showed no cortical or subcortical responses, while evaluation of brainstem auditory evoked potentials demonstrated a bilateral absence of all waves following the first one (i.e. of II, III, IV, and V waves). A blink reflex study confirmed brainstem involvement, showing bilateral absence of the R1 and R2 responses. Approximately four months after the brain injury, the patient underwent an 18F-fluorodeoxyglucose positron emission tomography study (FDG PET) that revealed a severe and widespread reduction of brain metabolism, except in the anterior regions of the frontal lobes (Fig. 3).

Written informed consent was obtained from the patient’s legal guardian for all procedures, and the study was approved by the local ethics committee.

**Discussion**

Coma is traditionally defined as a condition of unarousable unconsciousness due to dysfunction of the brain’s ascending reticular activating system (ARAS), which is responsible for arousal and maintenance of wakefulness (Young, 2009). The ARAS is a complex and diffuse network of neurons projecting from multiple brainstem nuclei to the cortex, via thalamic and extrathalamic pathways. In particular, ARAS brainstem nuclei project to the intralaminar nuclei in the thalamus, which in turn have diffuse activating

![Figure 2 - EEG results. A. EEG revealing low amplitude (<20 μV) background activity at 3-4 Hz (delta and theta bands). B. Epileptiform discharges with spikes and spike-waves associated with bilateral shoulder myoclonus. Intermittent epileptiform discharges and associated myoclonus were responsive to intravenous administration of benzodiazepines, without changes in the level of consciousness, suggesting that the epileptiform activity was not affecting the patient’s consciousness. At the time of the EEG recording, the patient was medicated with 2000 mg of levetiracetam per day. Both A and B are from an EEG recorded approximately nine months after the brain injury. Spontaneous electrical brain activity was recorded from 20 electrodes (O1, O2, O3, O4, P7, P8, Pz, T7, T8, C3, C4, Cz, T5, T6, F3, F4, Fz, F7, F8, Fp1, Fp2) placed in accordance with the International 10-20 System (band-pass, 0.5-70 Hz; sampling rate, 200 Hz). G2 is an arbitrary name for the common ear-linked reference. The impedance of the recording electrodes was monitored during data acquisition and was always below 5 kΩ. The last three channels (in red) show the horizontal and vertical electro-oculogram and the electrocardiogram. These channels have been added to reveal any ocular or electrocardiographic artifacts. Both pages in the figure encompass a recording period of 15 seconds.](image-url)
A poor outcome of coma occurs when either i) the entire multilevel system is involved in the context of an irreversible disruption of brain function (brain death), or ii) ascending arousal control is recovered, but not awareness, which is primarily dependent on the cortical regions (transition into UWS). The condition of the patient described in this report did not evolve in either of the above ways, as he remained in a comatose state. All the clinical, neurophysiological and neuroimaging data collected indicated massive brain damage involving the brainstem and the subcortical and cortical regions of the ascending wakefulness control system. An important point to note is that the patient's brain injury had a twofold cause, i.e. traumatic followed by hypoxic damage. This unusual condition probably led to both a disconnection of the ARAS brainstem nuclei from the thalamus and basal forebrain (typical of traumatic coma), and thalamic and cortical damage (typical of hypoxic coma). It is likely that, as a consequence, all of the major systems involved in wakefulness control were critically affected.

Clinical, neurophysiological and neuroimaging data suggest that LLC may constitute the most severe consciousness disorder, being a condition that falls just short of brain death. In this patient, FDG PET showed islands of preserved brain metabolism in the anterior regions of the frontal lobes. Although the patient's overall brain metabolism was severely depressed, these findings are different from those of brain death, in which FDG PET typically shows absence of neuronal function in the whole brain (Laureys et al., 2004). Thus, the term "long-lasting" should be preferred over "chronic" coma, as "chronic" implies that it is an irreversible condition and the current data still do not show this to be the case. We propose that LLC be considered a new category of disorder of consciousness, with clinical and pathophysiological features that differ from coma, UWS, and brain death (Table I). This condition should be assumed to be present when: i) a comatose state lasts more than 4 weeks (unlike coma), without any sign of recovery of ARAS functions (unlike what is seen in UWS), and ii) clinical, neurophysiological and neuroimaging data demonstrate massive brain damage in which both brainstem and cortical functions are severely affected, but not completely abolished (unlike what is seen in brain death). There is also likely to be bilateral involvement of the thalamus in LLC (Schiff, 2008). However, these concepts need to be confirmed by findings obtained from other cases.

The ethical issues raised by LLC are considerable. Given the peculiar features of this condition, specific ethical guidelines to govern the care of affected patients are mandatory. The need for such guidelines is even more pressing in the cases of patients who did not specify their end-of-life decisions. In accordance with current Italian law, the patient described in this report received all the essential care needed to support his life functions (i.e., mechanical respiration, artificial hydration and alimentation), to treat complications (i.e., infections), and to promote an improvement in his consciousness state (i.e., specific rehabilitation).

In conclusion, in this report we have described a case of LLC, a new type of disorder of consciousness resulting from a widespread disruption of the ascending arousal control system and characterized by persistence of a state similar to coma. We believe that this description may be useful for identifying other patients in LLC, in either intensive or post-intensive clinical settings. We also hope that this report will stimulate the scientific community to undertake studies aimed at identifying the prevalence of LLC, to...
define standard diagnostic criteria and to promote exhaustive debates about pathophysiological and ethical issues related to this condition.

References