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Case Report

Unexpected recovery from a vegetative state or misdiagnosis? Lesson learned from a case report

Antonino Naro, Rocco Salvatore Calabrò*, Patrizia Pollicino, Carmen Lombardo and Placido Bramanti
IRCCS centro Neurolesi "Bonino-Pulejo", Messina, Italy

Abstract.
BACKGROUND: Growing research is focusing on the identification of markers predicting recovery and demonstrating covert awareness in patients with chronic disorders of consciousness (DOC). Herein, we describe the case of a woman who emerged from unresponsive wakefulness syndrome (UWS) after four years, in whom an experimental protocol assessing brain connectivity predicted her awareness recovery, indicating a functional locked-in syndrome (FLIS) diagnosis.
CASE DESCRIPTION: A 68-year-old woman was admitted to our institute in 2012 in a UWS secondary to a severe brain hemorrhage, with a Coma Recovery Scale-Revised score of five. Her clinical conditions were stable for about two years, despite the intensive neurorehabilitation treatment. During hospitalization, she underwent a neurophysiological protocol demonstrating an extensive nociceptive processing within the pain matrix. After 3 years, our subject emerged from UWS, and then from minimally conscious state, being able to communicate properly.
DISCUSSION: Approaches investigating brain connectivity may be useful in DOC diagnosis and prognosis, highlighting residual brain networks subtending covert awareness. Hence, our case supports the necessity of taking into account FLIS diagnosis in DOC differential diagnosis and implementing paraclinical follow-up to intercept cases of possible, late recovery of consciousness, thus optimizing the most appropriate management and rehabilitative setting.

Keywords: Case report, misdiagnosis, disorders of consciousness (DOC), functional locked-in syndrome (FLIS), unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS)

1. Introduction

The neural correlates of consciousness, as well as the mechanisms supporting consciousness recovery, are not completely understood. This consequently compromises the accurateness of the diagnosis and prognosis of patients with disorders of consciousness (DOC) (Monti et al., 2010), including the unresponsive wakefulness syndrome (UWS) and the minimally conscious state (MCS), thereby raising thorny medical and ethical issues (Jennet, 2011).

Growing research is currently focusing on the identification of clinical, neurophysiological, and functional neuroimaging markers, predicting awareness recovery or demonstrating covert awareness, as in the functional locked-in syndrome (FLIS) and the UWS with the residual islands of consciousness (Bruno et al., 2011; Formisano et al., 2011a, 2001b, 2013). These entities are characterized by a residual large-scale cortico-thalamo-cortical connectivity,

*Address for correspondence: Rocco Salvatore Calabrò, IRCCS Centro Neurolesi "Bonino-Pulejo" S.S. 113, Contrada Casazza, 98124, Messina, Italy. Tel.: +3909060128954; Fax: +3909060128950; E-mail: salbro77@tiscali.it.

which allows only purposeful behavioural fragments that are less consistent than those observed in individuals with MCS. Therefore, patients with FLIS are often misdiagnosed as UWS by a clinical point of view. In this regard, the demonstration of a preserved but dysfunctional plasticity within large-scale networks sustaining complex sensory-motor integration processes may be a marker of covert consciousness as well as a predictive marker of consciousness recovery, given that such a preservation is a necessary prerequisite for consciousness to be generated and to emerge (Thibaut et al., 2012; Bagnato et al., 2013). Herein, we describe the case of a woman who emerged from a 4-year UWS, in which a connectivity assessment experimental protocol predicted awareness recovery and indicated a FLIS diagnosis.

2. Case description

A 68-year-old was admitted to our institute in 2012 in a UWS secondary to a large left hemispheric haemorrhage occurred after an episode of malignant hypertension. At the admission, our subject did not produce any single word, did not answer even to very simple requests (e.g., close your eyes) and did not communicate in any way, as showed by her Coma Recovery Scale-Revised (CRS-R) score of five (auditory function: 1, visual function: 1, motor function: 1, verbal function: 1, communication: 0, and arousal: 1) (T0). The neurological examination showed no voluntary movements, only reflex responses, reduction of the blink rate, spastic muscle tone, quadriparesis, and bladder and intestinal incontinence. Nuclear magnetic resonance imaging showed a large basal ganglia hematoma surrounded by toxic oedema and extending to ipsilateral ventricle with both sub-ependymal and free blood, yielding a mild midline shift.

Her clinical conditions and CRS-R scoring slightly improved over a period of two years (T24), during which she underwent a comprehensive, intensive rehabilitative therapy including sensory stimulation, physiotherapy, and computer assisted programs (e.g., the Neurowave). She was treated with baclofen, L-DOPA, and antiepileptic drugs.

2.1. Intervention

At T24, she underwent an experimental neurophysiological protocol (Laser-Paired Associative Stimulation, L-PAS), showing similar findings to those of the MCS individuals who were enrolled in the study. This fact demonstrated an extensive nociceptive processing within the so-called pain matrix, as suggested by the strengthening in pain-motor integration (PMI) (that reflects the functional connectivity within the pain matrix that supports pain perception) (Naro et al., 2015) (Table 1).

2.2. Outcomes

Our subject started to show some signs of emergence from UWS about one year after L-PAS application (T36) (i.e., three years from brain damage), beginning to respond to simple motor commands, show visual pursuit and then object recognition, and vocalize. Then, she gained full consciousness in a further period of about eight months (T44) (i.e., 44 months from brain damage), showing functional communication (i.e., emergence from MCS). Hence, our subject showed a progressive overall improvement, although in a framework of residual, severe motor (severe spastic tetraparesis) and mild cognitive disability (level five at the Rancho Level of Cognitive Functioning Scale). Even though PMI modulation preservation correlated with awareness recovery, we did not find a correlation between the magnitude of PMI modulation and of clinical scale improvement.

3. Discussion

The correct prognosis in patients with DOC is of paramount importance, since it allows better

Table 1
A summary of the case story and the L-PAS after-effects (percent change ± SD)

Time (months)	Age (years)	CRS-R	DOC diagnosis	L-PAS execution				
				MEP_{post} (%)	PMI_{pre} (%)	PMI_{post} (%)	NCS-R_{pre}	NCS-R_{post}
0	68	5	UWS					
24	70	5.3	UWS	119 ± 14	98 ± 8	115 ± 9	2	8
36	71	9	MCS					
44	71	20	EMCS					

DOC disorder of consciousness; L-PAS laser-paired associative stimulation; MEP motor evoked potential (% unconditioned MEP); PMI pain motor integration strength (% unconditioned MEP); CRS-R Coma Recovery Scale-Revised; NCS-R Nociception Coma Scale-Revised.

managing patient care and developing further patient-centred and -tailored therapeutic interventions, besides the ethical and psychological implications for the patient and the family (Liberati et al., 2014).

However, DOC prognosis is extremely challenging, given the uncertainness of DOC diagnosis and the fact that many prognostic factors come into play (e.g., other structural brain lesions than traumatic brain injury, metabolic and nutritional disorders, exogenous toxins, central nervous system infections and septic illness, seizures and *status epilepticus*, or hypo- and hyperthermia) (Haenggi et al., 2014). Although the clinical assessment remains of crucial importance, it suffers of some significant limits, as demonstrated by the cases in which patients who were classified as "irreversible" UWS emerged into MCS and further improved, even after years from brain injury (e.g., Arts et al., 1985). On the other hand, standardized testing may easily overlook the unusual phenomenological manifestations of covert awareness in individuals with severe neurological injuries. Thereby, advanced, para-clinical methods (functional neuroimaging and neurophysiology) may help clinician in both DOC diagnosis and prognosis.

Active approaches (i.e. those requiring patient's cooperation) demonstrated that the functional preservation of large-scale brain connectivity might be a good positive prognostic marker of a forthcoming consciousness recovery (Boly, 2011; Sharon et al., 2013; Sarasso et al., 2014; Gosseries et al., 2014). However, active cooperation in patients with DOC can be faint, owing to, e.g., cognitive decline or sensory-motor deficits rather than unconsciousness, so that a patient could be labelled as UWS at active paraclinical paradigm.

Our case report suggests that passive approaches investigating brain connectivity may be useful in DOC diagnosis and prognosis, beside clinical assessment. In fact, L-PAS induced vast electrophysiological modifications that usually rely on a residual large-scale brain functional connectivity, which is detectable in MCS rather than UWS individuals (Naro et al., 2015). Even though passive paradigms cannot offer any direct inference on awareness preservation, they highlight a brain connectivity that cannot be found usually in UWS individuals. Hence, we may argue a misdiagnosis in our subject, as she was affected by FLIS, in our opinion. This would also explain her atypical recovery pattern. In fact, she was clinically defined as UWS for two years and then emerged from UWS over one year and regained full consciousness in further eight months. Such uncommon pattern of awareness recovery (which is usually longer and variable, although exact definitions of time frames to estimate the outcome by clinical and neurophysiological examinations are still lacking) (Haenggi et al., 2014) may be justified by a misdiagnosis; in other words, our subject was in a FLIS that then emerged in a MCS. Indeed, FLIS is not so rare as intermediate phase of consciousness recovery and should be never neglected in DOC differential diagnosis (Bruno et al., 2011; Formisano et al., 2011a, 2001b, 2013).

Noteworthy, such large network residual plasticity and connectivity may represent the basis on which constructing cortical responses to painful stimuli at conscious level (Whyte, 2008), thus representing a prognostic marker of possible consciousness recovery. In fact, our subject gained full consciousness in the following 20 months, as compared to the other patients with UWS who instead lacked the plasticity markers showed by our subject (Naro et al., 2015). However, the time span between electrophysiological and clinical awareness recovery is unpredictable, since PMI magnitude following PAS does not foretell the time required regaining full consciousness (Naro et al., 2015).

4. Conclusion

Even if promising, data coming from paraclinical approaches should be handled carefully. In fact, these approaches are only investigational, employ often active paradigms that require patient's participation (that can be challenging owing to the limited cooperation ability by the patient), and seem difficult to be incorporated into clinical medical practice (Boly, 2011). In addition, the repeatability and validity of such approaches in terms of proving the diagnosis and delineating the prognosis need to be confirmed by future studies.

In conclusion, our case highlights the necessity of taking into account FLIS diagnosis in DOC differential diagnosis and implementing paraclinical follow-up to intercept cases of possible, late recovery of consciousness, thus optimizing the most appropriate management and rehabilitative setting.

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Written informed consent to case description was obtained from the subject.

Conflict of interest

The authors declare neither conflicts of interest nor financial support.

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