Outcome predictors for patients with prolonged disorders of consciousness

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Clinical evolution of prolonged disorder of consciousness

Over time, the temporal frameworks for regaining consciousness following a severe acquired brain injury (sABI) have undergone refinement. After a comatose state due to traumatic or non-traumatic sABI survivors may remain in a clinical condition of wakefulness without awareness, known as vegetative state [28], recently named unresponsive wakefulness syndrome (VS/UWS; [23]). If patients regain minimal, inconsistent but clearly discernible clinical signs of intentional/conscious responses to standardized stimuli, this can be classified as minimally conscious state (MCS; [17]). Based on the complexity of their behaviors, the MCS patient can be classified as MCS minus (low-level intentional behavior, such as visual pursuit of salient stimuli) or MCS plus (high level of behavioral interactions, such as language comprehension and command following) [2]. If these three clinical conditions (i.e., VS/UWS and MCS minus and plus) – named as prolonged disorder of consciousness (pDoC) – last more than 28 days after brain injury [16] they are often transitional states between coma and full recovery of consciousness **(Fig. 1)**. However, some patients can remain in a chronic condition of DoC, even for a lifetime. Some other patients do recover full consciousness after the classical time limits suggested by the Multi Society Task Force on VS (i.e., 12 months after traumatic brain injury and 3 – 6 months after vascular and anoxic brain injury; 28), especially in younger patients [5–7, 9–11]. However, these "late recovered" patients do not recover functional motor and cognitive abilities to the same extent, and their (and their family's) quality of life is poor [7].

Additionally, new categories of patients with covert cognition or covert awareness or cognitive motor dissociation have been identified, which present challenges in prognostication [4,32]. These patients are about 30 % of patients clinically classified as in VS/UWS in whom advanced tools, such as functional brain-imaging techniques, detect residual cortical activation suggestive of residual conscious processing [4, 32, 33]. Although the clinical evolution of these new diagnostic categories has not been established yet, the presence of covert cognition seems to have important prognostic significance, as it is a sign of positive clinical evolution. However, the recognition of these diagnostic groups can be challenging, as advanced neuroimaging or neurophysiological tools cannot be applied in all patients due to technical problems (such as patient agitation, presence of mechanical ventilation). In addition, although recommended by the European Academy of Neurology guidelines for the diagnosis of patients with DoC [22] these tools are not widely available in routine care, due to logistical problems or lack of expertise.

What happens when the patient emerges from pDoC? The big database of the traumatic brain injury model system identified 4 distinct prognostic subgroups of patients with different trajectories of recovery of self-care, mobility and cognition and some of them showed robust recovery over time even until 10 years from injury [19]. These findings strongly suggest that individuals with pDoC may benefit from ongoing functional monitoring and updated care plans for at least the first decade.

The mesocircuit forebrain encompassing projections from the central thalamus and basal ganglia to the cortex is the main area disrupted in severe brain injury and shows functional changes during recovery of consciousness, as revealed by functional neuroimaging of neurophysiological evaluation [30]. These findings seem to confirm that these supratentorial structures can be target areas for neurorehabilitation or neuromodulation. Furthermore, the transition from MCS minus to MCS plus is associated to an increase in brain metabolism of the specific areas involved in language processing, such as left fusiform, angular area, and temporal cortex [1].

Additionally, the pivotal role of thalamus in the consciousness recovery has been confirmed by the quantitative analysis of Electroencephalography (EEG). The "ABCD" model identified a sequential change in EEG power spectrum during recovery of consciousness through four coarse-grained categories, which reflect the status of thalamocortical dynamics and the gradual restoration of resting membrane potential of neocortical neurons due to reafferentation by ascending arousal network and co-activation of mesocircuit network [31]. In the evolution from coma to full recovery of consciousness the EEG analysis revealed: 1. pattern A in patients in VS/UWS (i.e., EEG power spectrum <1 Hz) in which neocortex is completely or almost completely deafferented and the neocortical neuron show marked hyperpolarization; 2. pattern B in patients in VS/UWS, MCS results from an intrinsic oscillation of the cortical pyramidal cells (i.e., EEG power spectrum 5–9 Hz);

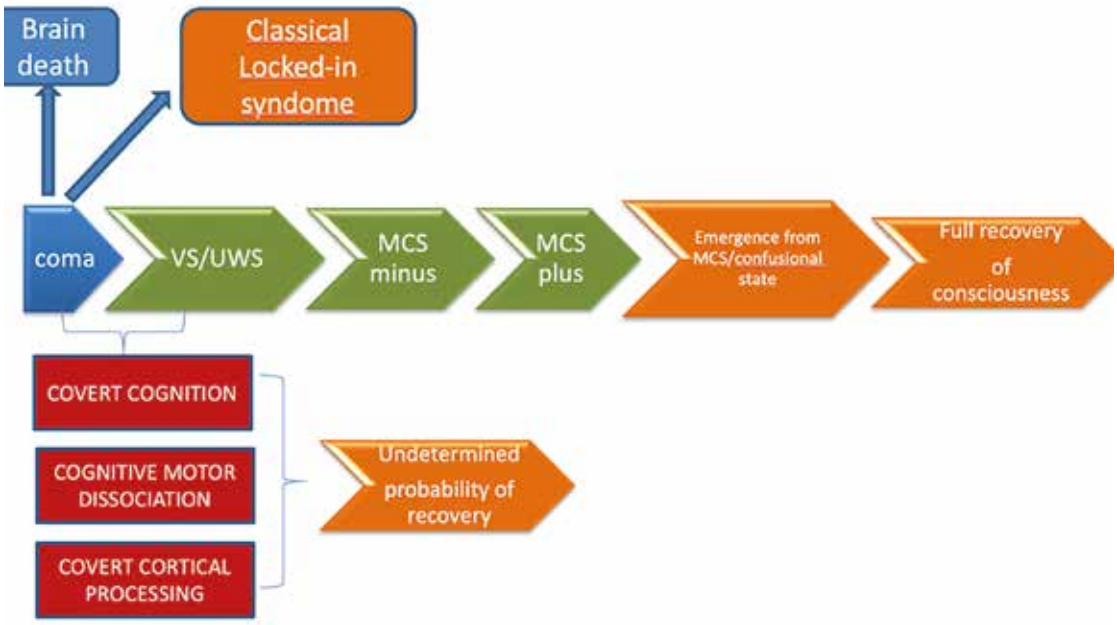

Figure 1. Clinical evolution of patients with disorder of consciousness. **VS/UWS** vegetative state/unresponsive wakefulness syndrome; **MCS** minimally conscious state

3. pattern C in MCS or conscious patients corresponding to a partial restoration of neocortical potentials and thalamic bursts; and 4. pattern D refers to a restoration of the normal EEG power spectrum with a peak in the alpha frequency range (8–13 Hz) and peaks in higher frequency ranges are associated with normal neocortical neuronal firing in healthy individuals [30, 31] **(Fig. 1).**

Gaps in the Prognostication of Prolonged Disorders of Consciousness

When discussing prognostication of patients with pDoC, it is crucial to acknowledge the pervasive climate of uncertainty. Despite the extensive body of literature addressing the diagnosis and treatment of pDoC, there exists a notable dearth of comprehensive reviews and data regarding prognosis in this patient population. This gap could be ascribed to the difficulties in longitudinally following this complex population that most often are lost after the acute or rehabilitative phases [12]. Recently, The American Academy of Neurology provided few recommendations for prognostication of adult persons with pDoC [16]. However, implementing them in practice remains challenging [13], and the prognostic procedures for people with pDoC vary across countries and might result in differences in patients' management and outcome [15]. For example, neurophysiological tests, which are very informative for prognosis, are used more frequently in European countries than in the United States [15]. In this context, even today, physicians and patients' families still face many difficulties in making appropriate decisions on long-term care of such complex patients.

Predictors for Neuroprognostication

Various predictors, categorized as conventional markers (i.e., easy to collect at the patient's bedside) and emerging markers (i.e., collected using advanced techniques) have been identified [14]. Both conventional and emerging prognostic markers present numerous pitfalls and biases that make the results difficult to interpret or translate into clinical practice. Among them, the most common is the self-fulfilling prophecy (i.e., when discontinuation of life sustaining therapy itself produces an unfavorable outcome and confirms initial predictions). Moreover, in most longitudinal studies the number of deaths due to treatment discontinuation is not clearly reported. Additionally, the prognostic studies show several biases, such as heterogeneity in patient population, protocols, follow-ups, and outcome measures [12, 14]. In this context, the prognostication at individual level must be done with caution.

Notwithstanding these limitations, some predictors can help clinicians to plan the most appropriate care pathway in terms of intensity and duration of neurorehabilitation treatment.

The first clinical predictor is the clinical diagnosis, as clinical evolution in the short, long and very long-term is better in MCS than in VS/UWS patients [9–11, 26], likely due to low severity of brain damage and to better response to the treatment that has been found in MCS patients [8]. Also, the level of responsiveness as measured by the Coma Recovery Scale Revised total score (CRS-R; 18) can predict mortality and consciousness recovery at 12 months [3, 9–11].

More recently a machine learning approach using all CRS-R domains simultaneously identified a new consciousness index (i.e., from the interaction of all CRS-R sub-scales) in a cohort of 190 patients with pDoC [24]. This consciousness index showed a higher predictive value then the clinical diagnosis and CRS-R total score [27]. However, issues in recognizing patients with covert cognition may make it difficult to use these clinical markers as predictors.

The conventional neurophysiological evaluation of patients with pDoC can help clinicians in prognostication. The bilateral absence of the N20 cortical component on somatosensory evoked potentials is a robust predictor, especially for poor outcomes and anoxic patients, which can be recorded not only in the acute phase [29], but also in the post-acute phase [6]. However, the preservation of N20 component does not imply a favorable outcome, as patients with presence of N20 may have different outcomes. This discrepancy could be explained by the fact that the generation of the N20 component in the somatosensory cortex has a lower metabolic demand with respect to the intracortical synaptic transitions, recorded by the standard EEG. Based on these considerations, patients with severe brain damage (i. e., with severe disruption of cortical synaptic) can show suppressed EEG background, but preserved N20 [35]. Additionally, visual analysis of conventional EEG (easy to record at bedside and in all settings) can be informative in the neuroprognostication, as presence of EEG background reactivity is associated with a 5-fold higher probability to recover consciousness [11], whereas a poor EEG background activity is significantly associated with a higher risk of mortality in MCS group [10].

Among advanced technologies, the FDG-PET seems to be more informative as a higher metabolic index in the best-preserved hemisphere is associated to higher level of consciousness, thus allowing to detect covert cognition and to predict 6-month command-following recovery in VS/UWS with high FDG-PET metabolism [20].

Conclusion

A basic multimodal prognostic protocol, including clinical and neurophysiological assessment at the patient's bedside, is recommended for planning the course of care of patients with pDoC in different settings and countries. The integration of advanced tools (e.g., PET, resting-state fMRI and quantitative high-density EEG analysis), together with accurate behavioural assessment, may allow the detection of hidden cognition and improve prognostic accuracy. International consensus and guidelines for prognostic procedures in patients with pDoC are needed to standardise prognostic procedures in clinical practice in different countries.

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