A twitch of consciousness: defining the boundaries of vegetative and minimally conscious states

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Some patients awaken from their coma but only show reflex motor activity. This condition of wakeful (eyes open) unawareness is called the vegetative state. In 2002, a new clinical entity coined "minimally conscious state" defined patients who show more than reflex responsiveness but remain unable to communicate their thoughts and feelings. Emergence from the minimally conscious state is defined by functional recovery of verbal or non-verbal communication.[1] Our empirical medical definitions aim to propose clearcut borders separating disorders of consciousness such as coma, vegetative state and minimally conscious state but clinical reality shows that these boundaries can often be fuzzy (fig 1). Recent clinical, electrophysiological and neuroimaging studies are shedding light on these challenging limits of consciousness encountered following severe acute brain damage.

At the patient's bedside, it is very challenging to differentiate reflex or automatic motor behaviour from movements indicating signs of consciousness, and hence some minimally conscious patients might be misdiagnosed as being vegetative. For some motor responses (eg, blinking to visual threat, brief fixation, normal flexion response to pain, etc) it remains unclear whether they truly are voluntary or willed because we lack convincing scientific evidence. We also lack consensus on how to practically assess some of these behavioural responses. For example, there is no agreement on what stimulus to employ in the assessment of visual pursuit movements—often one of the first clinical signs heralding the transition from the vegetative to the minimally conscious state. Vanhaudenhuyse and colleagues[2] recently studied visual pursuit in 51 post-comatose patients comparing eye tracking of a moving object, person or mirror. It was shown that more than a fifth of the minimally conscious patients with visual pursuit only tracked when studied by means of a moving mirror and not when studied by means of a moving object (ie, the stimulus most frequently used in our routine neurological examination) or by means of a moving person. Such behavioural studies permit improvement in the challenging behavioural assessment and diagnosis of severely brain damaged patients.

At present, the clinical examination remains the gold standard in defining the boundaries of disorders of consciousness. However, similar to the role of confirmatory para-clinical tests in brain death, validated objective markers of consciousness could improve our diagnosis of vegetative and minimally conscious states. In this issue, Bekinschtein and colleagues[3] investigated command following (ie, "move your hand") while recording EMG activity in eight patients with the clinical diagnosis of the vegetative state (only patients with preserved withdrawal reflex and preserved auditory evoked potentials were included) ***(see page 826)***. In one such patient (studied 3 months after a traumatic brain injury and with only mild cerebral atrophy on MRI), significant command related sub-behavioural threshold EMG changes were demonstrated. This finding indicates that the patient understood the task (no EMG changes were seen when a "do not move" command was presented) and repeatedly performed the task during a sustained period of time (ie, 30 s). Hence, the reported patient, clinically diagnosed as vegetative, was conscious.

The proposed methodology is comparable—albeit much simpler, cheaper and portable—to the functional MRI methodology validated by Boly *et al* measuring blood oxygen level dependent cerebral activation in non-communicative patients.[4] Using this functional MRI technique, Owen *et al* objectively showed signs of consciousness in a patient (studied 5 months after trauma) with the diagnosis of the vegetative state.[5] These studies are clinically and ethically important, as the careful and controlled complimentary examinations changed the patient's bedside diagnosis. The next challenge will be to adapt this technology such that it permits the patient to communicate his or her views and feelings (ie, thought translation devices or brain computer interfaces). The patient reported by Bekinschtein and colleagues[3] recovered brief fixation and unintelligible vocalisation but failed to show any functional communication at the time of writing (12 months post-injury). Such behaviourally unresponsive patients, only showing identifiable signs of consciousness by means of sophisticated electrophysiological or neuroimaging techniques, will challenge our current standards for care and end of life decision making paradigms. It should, however, be emphasised that the reported patients suffered a traumatic brain injury and were studied within 6 months after injury.[3 5] Convincing signs of consciousness have so far never been reported in the post-anoxic vegetative state.

In addition to the boundaries defining emergence from the vegetative state, the upper boundaries defining minimally conscious patients have been challenged. Recently, Nakase-Richardson and colleagues[6] studied the clinical criteria for emergence from the minimally conscious state—that is, functional interactive communication—operationally defined as accurate yes/no responses to six of six situational orientation questions on two consecutive evaluations.[1] Having performed standardised cognitive testing in 336 responsive patients recovering from traumatic brain injury, the authors conclude that these criteria might be too

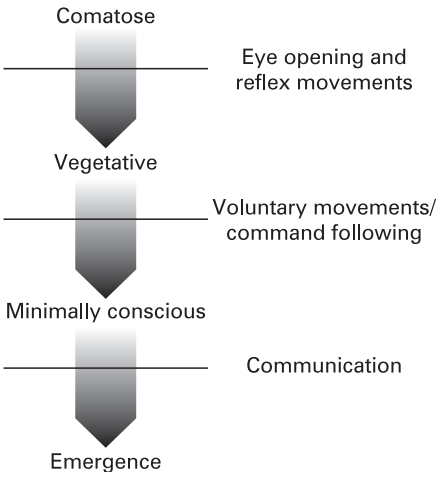

Figure 1 Drawing sharp borders behaviourally, defining the progressive transitions from coma, to vegetative state, to minimally conscious state, to emergence from the minimally conscious state, remains very challenging. Recent studies are shedding new light on the boundaries of these disorders of consciousness.

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tough. Our understanding of residual cognition in post-comatose states remains limited but studies such as those mentioned above are offering the scientific evidence that will redefine the contours of altered states of consciousness encountered after severe brain damage.

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Hu, Yo, Ri, Ma, Ta: monosyllabic answers to complex questions

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Patients' names rarely obtain a prominent place in medical history. The exotic abbreviations from the title are an exception, as some patients, who presented with a rare but intriguing neurological syndrome, lend the first two letters of their names to indicate the antigen involved in their autoimmune disease. The search for autoantibodies related to limbic encephalitis is a successful example. Anti-Hu, anti-Ma, anti-Ta and anti-NMDA receptor antibodies were discovered as paraneoplastic antibodies in patients with tumours such as lung, testicular cancer or ovarian teratomas.[1 2] Antibodies to voltage gated potassium channels, infrequently associated with cancer, were shown to be associated with a treatable form of limbic encephalitis.[3] In this issue of *J Neurol Neurosurg Psychiatry*, Hoffmann and colleagues[4] expand the spectrum of paraneoplastic neurological diseases by giving a detailed description of the neurological presentation of patients with anti-Ma or anti-Ta antibodies ***(see page 767)***. These antibodies are members of a series of specific antibodies, the presence of which strongly suggest, if not prove, the presence of a tumour in patients with typical neurological diseases. Anti-Ma or anti-Ta antibodies appear to be highly specific markers for the underlying tumour, even to the extent that an orchiectomy has been performed in patients based only on the neurological signs and symptoms in combination with anti-Ta antibodies.[5]

From the moment a specific antigen has been discovered, its recombinant protein allows testing of large numbers of sera which help to delineate the borders of the clinical syndromes associated with the particular antibody. Hoffman *et al* succeeded in finding 22 new patients with anti-Ma or anti-Ta antibodies.[4] They confirmed the specificity of anti-Ta antibodies and their association with limbic encephalitis and testicular cancer in young male patients. The majority of the anti-Ma positive patients also had a limbic or brainstem encephalitis, but the sex distribution was equal. Interestingly, they were associated with a broad range of tumours, in contrast with most other paraneoplastic antibodies. For the first time, they also described involvement of the peripheral nervous system in four patients with polyneuropathy or motor neuron disease. These observations, however, need further confirmation. In one patient, the polyneuropathy could also be explained by the overlap with an anti-Hu syndrome. In two patients there was no clear tumour association, and in an anti-Ta positive patient the polyneuropathy developed 14 years after a testicular germ cell tumour, which weakens a causal relationship. The results could also suggest that these antibodies might be present in idiopathic non-tumour related neurological autoimmune diseases. For membrane bound antigens such as the voltage gated potassium or calcium channels, non-paraneoplastic forms of the associated disorders are well known. To date, the paraneoplastic intracellular antigens such as Ma and Ta, but also Hu, Yo or Ri, are very rarely associated with idiopathic autoimmune diseases.

Not only are these antibodies extremely useful for diagnostic purposes, but their existence also confirms that a powerful antitumour immune response is possible. Several reports suggest that the immune system can retard tumour growth to an extent which is far greater than any chemotherapy has achieved, or can even completely eliminate the tumour. One would expect that the identification of the antigens involved in these diseases should boost the development of immune therapies, but dissecting the pathophysiology of the immune response in these patients has proven quite difficult. With the renewed interest in immune therapies for several forms of cancer and the advances in immunogenetic techniques, it is now time to bring this one step further.

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