

Minimally Conscious State: Evolution of Concept, Diagnosis and Treatment

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ABSTRACT

The study of consciousness disorders is a scientific challenge, and clinical differentiation among the various sorts of alterations in consciousness is difficult. Persistent vegetative state was defined in 1972, but years later cases appeared in which diagnosed patients showed signs of cognitive activity, and therefore could not be considered vegetative. Minimally conscious state was defined in 2002. This article discusses minimally conscious state based on a literature review and the author's clinical experience. A brief historical outline is given, starting from 1886 when Horsley analyzed level of consciousness. The article reviews criteria for defining minimally conscious state, as well as the differential diagnosis from persistent vegetative state, brain death, coma, locked-in syndrome and akinetic mutism. Modern discoveries of residual cognitive functioning and new neural correlates have contributed to increased knowledge of this condition. Regardless, minimally conscious state continues to be a challenge for neuroscientists around the world, with issues still to be resolved.

KEYWORDS Consciousness, consciousness disorders, minimally conscious state, persistent vegetative state, coma, akinetic mutism, brain death, neurosciences, locked-in syndrome, coma, Cuba

HISTORY

Consciousness has long been a controversial topic. In 1886, Horsley, a philosopher and England's first neurosurgeon, asserted that levels of consciousness were related to the health and functioning of the cerebral cortex, and also established that the neopallium differentiates man from other animals.[1] At the end of the 19th century, Ramón y Cajal discussed the cortex (without relating it to consciousness), describing its appearance as that of a densely populated forest of trees (pyramidal cells), which, when intelligence was nurtured, could multiply their branches, deepen their roots and bear ever more varied and exquisite flowers and fruits.[2]

In 1940, Kretschmer, a German neurologist and psychiatrist, stated that the cortex was not necessary for arousal or for sleep-wake cycles. He correctly believed that these states could be present if brainstem functions were preserved, even if there was massive loss of cortical functioning (absence of neocortex or pallium).[3] At the time, consciousness was believed to be exclusively dependent on the cortex, whose compromise constituted severe brain damage.[4] In 1958, French researchers suggested the terms "prolonged coma" or "prolonged unconsciousness" to refer to the state of some patients with no voluntary responses whatsoever for many months following severe brain injury.[5]

In 1972, *The Lancet* published "Persistent Vegetative State after Brain Damage: A Syndrome in Search of a Name,"[6] perhaps the most important work on the subject at the time, written by two prestigious neuroscientists, British neurosurgeon Jennett,

codeveloper of the Glasgow coma scale, and US neurologist Plum, coauthor of the seminal text, *Stupor and Coma*. [7]

In 1994, the Multisociety Task Force on Persistent Vegetative State (MSTF)[8] defined specific criteria to diagnose a patient as being in persistent vegetative state (PVS). These were initially well received, and the old diagnostic categories of "apallic syndrome," "neocortical death," "neomort" and "coma vigilans" fell into disuse. However, years later, patients began to be diagnosed who were unconscious but did have a sleep-wake cycle and some cognitive activity, and therefore did not meet MSTF criteria for PVS.

Prestigious scientific institutions formed working groups to address the issue and differentiate patients with evidence of cognitive activity from patients in PVS. The American Academy of Physical Medicine and Rehabilitation suggested calling it *minimally responsive state*[9] but the International Work Group at the Medical College of London considered *low state of consciousness* to be a better choice.[10] Later, a working group of the American Society for Parenteral and Enteral Nutrition suggested calling it *minimally conscious state* (MCS),[11] which has remained the most commonly accepted term.

No scientific evidence specific to MCS was published until 2002, when the American Academy of Neurology commissioned a working group, led by Giacino, to develop a definition and diagnostic criteria. The group conducted a MEDLINE search using the keywords coma, vegetative state, minimally responsive state, stupor, Glasgow coma scale, late recovery and severe handicap. Only 5 of 260 abstracts containing ≥ 1 of these terms reported manifest differences between patients in PVS and MCS. After rigorous analyses during nine systematic scientific meetings, a consensus was finally reached for definition of MCS.[12]

DEFINITION AND DIAGNOSTIC CRITERIA

MCS is a neurological condition characterized by a serious alteration of consciousness. However, patients show clear and repeated signs of awareness of themselves or their environment.[12]

The following criteria have been established for MCS diagnosis:[12]

- following simple commands
- yes/no responses (gestural or verbal)
- intelligible verbalization
- purposeful, not just reflexive, behavior in response to an environmental stimulus, such as
 - appropriate smiling or crying in response to an emotionally meaningful auditory or visual stimulus
 - vocalization or gestures in direct response to questions
 - reaching for objects that demonstrates a clear relationship between the position of the object and the direction of the movement
 - touching or holding objects
 - following or staring at an object in direct response to its movement

DIFFERENTIAL DIAGNOSIS

Other alterations of consciousness—primarily PVS, coma, brain death, locked-in syndrome and akinetic mutism—must be assessed in order to make a differential diagnosis. PVS, which is most commonly confused with MCS, is characterized by a complete absence of awareness of oneself and one's environment, with a sleep–wake cycle, and partial or total preservation of hypothalamic and brainstem autonomic functions.[6,13] Patients with PVS differ from those with MCS in that they are not able to follow simple commands, do not display intelligent verbalization, and their gaze does not track objects in direct response to movements. Experience shows that if these patients are examined without applying MSTF criteria,[8] there could be diagnostic errors in diagnosis.

In coma, arousal and spontaneous eye opening are absent and there is no sleep–wake cycle or awareness of oneself or the outside world. Coma patients do not show signs of response to or comprehension of language and expression. They may recover or progress to brain death, clinical death, or PVS or MCS.[14]

Brain death is the irreversible loss of all brain function.[14] If life is understood as the active state of organisms represented by the brain, we cannot talk about life without brain activity. Brain death is, therefore, true death, the point of no return, as I argued in a recent article.[15] Its differential diagnosis from MCS lies in the fact that brain-dead patients do not follow simple commands, cannot produce yes or no responses or intelligible verbalization. The legal implication of this distinction is that brain-dead patients' organs and tissues may be used for transplants, but not those of patients with MCS. The important bioethical implications of this are beyond the scope of this article.

Locked-in syndrome is a state in which a selective loss of supranuclear afferent motor fibers causes paralysis of the four limbs and inferior cranial nerves, without loss of consciousness. Patients with locked-in syndrome are not able to move their limbs, nor make gestures, unlike MCS patients, but can make vertical eye movements, enabling them to communicate. Akinetic mutism is a state in which a patient is unable to move or speak, but appears to be alert. Like MCS patients, persons with akinetic mutism have sleep–wake cycles, but they lack spontaneous motor activity, which is present in MCS.[14]

TREATMENT AND CLINICAL COURSE

There is no definitive consensus regarding treatment. Options are classified as pharmacological and nonpharmacological. There are two categories of pharmacological treatment: nervous system depressants (zolpidem, lamotrigine and baclofen) and stimulants (amantadine, amphetamine, apomorphine, bromocriptine, levodopa, methylphenidate and pramipexole). The best results are seen with zolpidem, an imidazopyridine or nonbenzodiazepine hypnotic[16,17] that works by selectively stimulating GABA_A receptors (BZ-1 or omega 1 subtype).[1,17] One of its advantages is that it can be used in patients with respiratory disorders or chronic obstructive pulmonary disease, because it has no respiratory side effects.

An example of nonpharmacological treatment is deep brain stimulation, which consists of implanting an electrode within the brain, usually in the thalamus, in order to reactivate connectivity between anatomical areas that support communication and purposeful behavior. The isolated cases published on deep brain stimulation for MCS are not convincing evidence for its use as definitive therapy.[18,19]

Multimodal sensory stimulation and sensory regulation aim to stimulate all senses separately at a controlled frequency in order to enhance synaptic reinnervation and accelerate neurological recovery. They also seek to prevent sensory deprivation and facilitate the connection between the brain and sensations in different parts of the body. Individualized physical and occupational therapies are used in rehabilitation centers to prevent complications[20] and can be beneficial in rehabilitation.[21]

It is especially important to pay close attention to general supportive care, including hydration, nutrition, ventilation and hygiene, and to early detection of intercurrent infection and bedsores. Good general care for MCS patients requires a multidisciplinary team, comprising the attending physician, nursing staff, physical therapist and psychologist. Close collaboration among these professionals, together with the family, will greatly favor the patient's progress. A personalized, comprehensive treatment plan should be established, specific to each individual's needs and depending on the cause of their condition.[21,22]

If pharmacological and nonpharmacological treatments are administered successfully, patients with disorders of consciousness may see improvements in their status. In a 3-year followup study of PVS patients, the following results were found: at 3 months, 81.1% (30/37 patients) remained in PVS and 8.1% (3/37) progressed to MCS; at 6 months, 40.5% (15/37) remained in PVS and 29.7% (11/37) progressed to MCS; at 1 year, 24.3% (9/37) remained in PVS and 75.7% (28/37) died; and at 3 years, 10.8% (4/37) remained alive in PVS.[15]

In our case series in Cuba, serious brain injury was the cause of PVS in all patients who progressed to MCS. Our results suggest that the first six months are critical, since there was no improvement after this period.[15] However in a recent case study from the UK, a man aged 29 years entered PVS after a serious brain injury and after 15 months progressed to MCS, from which he emerged after four months. Three years after his initial injury he was moderately disabled and living in the community, with support. The authors emphasized the importance of early intensive multidisciplinary rehabilitation to stimulate unaffected brain areas that can substitute lost functions through neuroplasticity.[23] (a subject that also extends beyond the scope of this article).

RECENT STUDIES AND PROJECTIONS

De Salvo's neurophysiology studies used evoked potentials induced by neurosensory stimulation and compared residual cognitive function in patients with MCS and PVS. She found significant changes only for the P300 wave, not the N100 and N200. This pilot study opens new lines of research in the quest to improve diagnosis, treatment and rehabilitation and to identify useful prognostic markers.[24] Also in the realm of residual cognitive activity,

Chinese scientists analyzed the arithmetic skills of PVS and MCS patients by using a hybrid brain-computer interface and training patients to process numbers and mathematical calculations.[25] The P300 wave results are similar to those found by De Salvo.[24] Italian neuroscientists have significantly preserved olfactory neuronal activity through activation of the pyriform cortex in 100% of MCS patients, versus 58% of PVS patients.[26] Also in Italy, Varotto's EEG study of 18 patients found significantly decreased delta wave connectivity, while alpha activity was hyperconnected in the central and posterior cortical regions.[27] Fingelkurts obtained similar EEG results and found that fast alpha waves are unique to MCS, while delta, theta and slow alpha waves are more frequent in PVS.[28]

MRI spectroscopy is useful in monitoring biochemical changes, specifically, the concentration of N-acetyl-aspartate and creatine, which are indicators of neuronal integrity. Yang found a significant increase in NAA/Cr ratio in the cerebral cortex in patients who progressed from PVS to MCS, while it decreased in patients who remained in PVS.[29]

Consciousness is an integrated function involving neural networks of the cortex, thalamus and subcortical-cortical system. Sound scientific evidence exists of the neural correlates of con-

scious and unconscious processes.[27] Mura demonstrated them through variations of alpha waves and the N100 potential amplitude in patients who received transcranial electrical stimulation. [30] Gosseries reported similar results in 2014 using the same methods with another sample of patients.[31]

Research efforts are currently aimed at the following areas: incidence and prevalence, natural history and recovery path, neuroimaging studies, validation of diagnostic criteria for the physiopathological mechanisms involved in disorders of consciousness, differences between adults and children in clinical course and recovery, cause-specific clinical course, predictive factors, and treatment efficacy.

CONCLUDING REMARKS

MCS is a clinical condition characterized by markedly diminished consciousness with clear and reproducible signs of awareness of oneself or the environment. Modern discoveries of residual cognitive functioning and new neural correlates have increased understanding of this condition. Despite this, MCS continues to present a challenge for neuroscientists, involving many unanswered scientific and clinical questions requiring further research to help find better solutions for patients in MCS. 

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