THE MINIMALLY CONSCIOUS STATE (MCS) AND RELATED DISORDERS OF CONSCIOUSNESS: DEFINITIONS, DIAGNOSTIC CRITERIA, NATURAL HISTORY AND PROGNOSIS

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Introduction

Over 30 years ago Jennett and Plum (1972) introduced the term, *vegetative state* to describe a well-recognized syndrome in which patients are awake but unaware. They subtitled their paper, "a syndrome in search of a name." Subsequently, the vegetative state has become an accepted, if not somewhat controversial diagnostic term, and diagnostic guidelines have been developed. Diagnosis and prognosis of the vegetative state have been addressed by the Multi-Society Task Force on PVS (1994) subsequently by the American Academy of Neurology practice parameter (1995). These papers stopped at the clinical boundaries of the vegetative state (VS). They distinguished VS from clinically related conditions, such as coma, brain death, locked-in syndrome and akinetic mutism, but did not address states of partial conscious awareness. The Multi-Society Task Force as well as Jennett and Plum posited an absolute distinction between those patients who never show signs of consciousness and those who may show evidence of inconsistent or low levels of conscious awareness. In the Multi-Society Task Force statement, patients with behavioral responses beyond the criteria of the vegetative state were described in terms of the functional outcome labels used in the Glasgow Outcome Scale (Jennett & Bond, 1975) – i.e. *severe disability, moderate disability*. The neurological aspects of these conditions of emerging consciousness were not discussed.

It has been widely recognized that many patients display a clinical condition that does not fit the criteria for vegetative state (VS) or complete unconsciousness, however these patients cannot be considered fully conscious (Andrews, 1996; ACRM, 1995). This clinical state may occur during the transition between unconsciousness and consciousness, or as a fixed, persistent condition in those with profound brain damage. A number of commonly used clinical scales address the transition to these levels (e.g. the Rancho Los Amigos scale [Hagen et al, 1972], Glasgow Coma Scale [Teasdale & Jennett, 1974], Coma-near coma scale [Rappaport et al, 1992], Coma Recovery Scale [Giacino et al, 1991]). This too became 'a syndrome in search of a name'. Several workgroups grappled with defining this clinical state (American Congress of Rehabilitation Medicine (ACRM) Interdisciplinary Special Interest Group for Head Injury [1995]; International Working Party on the Management of the Vegetative State [Andrews, 1996] and the Aspen Neurobehavioral Conference Workgroup [Giacino et al, 1997]). The ACRM group (ACRM, 1995) proposed the term, *minimally responsive state* and the International Working Party used *inconsistent low awareness state* in addition to various gradations of the vegetative state (Andrews, 1996). More recently the Aspen workgroup, made up of representatives from neurology, neurosurgery, physiatry, neuropsychology, nursing, allied health and bioethics, recommended the term *minimally conscious state* (Giacino et al., 2002).

All of these groups recognized the need for more precision in the diagnosis of different levels of impaired consciousness. The distinction between *vegetative* and *minimally conscious states* is important because prognosis and treatment choices may be different for these two conditions. Decisions regarding withdrawing fluid and nutrition, continuing medical or rehabilitative treatment, or managing pain and suffering might hinge on the differentiation of unconsciousness and minimal consciousness. Further, scientific study of severe alterations of consciousness requires uniform and precise definitions of these clinical states to allow replication and comparisons across studies. The transition between “unconscious” and “conscious” states is not always easily recognized, especially in patients whose neurological course (improvement or deterioration) is evolving slowly. Diagnostic accuracy for the *vegetative state*, distinguishing it from the *minimally conscious state* and other related conditions has been less than ideal (Childs et al., 1993; Andrews et al,1996).

The Challenge of Defining Consciousness

Defining consciousness has historically been an elusive endeavor. Widely accepted definitions of consciousness often include some reference to *awareness* of self and the environment (Plum and Posner, 1980; James, 1890) or the brain’s ability to form a unified representation of the world, our bodies and ourselves (Hobson, 1997). William James (1890) (and more recently others such as John Searle [1992], Thomas Nagel [1986]; Antonio Damasio [1999]) emphasized several properties of consciousness including: its *personal* aspects, unique to the point of view of the conscious individual; its *constantly changing* characteristics, stable for only short periods of time; its *continuity*, linking consciousness of the past with consciousness of the present; its *selectivity* and *finite* capacity to attend to the array of stimuli presenting to the nervous system at any moment.

These definitions of consciousness provoke further questions, including what constitutes “awareness” and how much awareness is sufficient to attribute “conscious awareness.” Does consciousness depend on the quantity or level of complexity of cognitive processing, or are there particular qualities of cognition that constitute the essence of consciousness? Complexity of processing may range from basic sensation to cognition of self and environment in the context of time. Complexity of processing varies considerably from lower animals to humans, from infants to adults, and even, at different times, in fully conscious adult humans. Are infants or nonhuman animals fully conscious?

Various authors have grappled with these questions and proposed hierarchical levels of consciousness and awareness. These levels may range from gross wakefulness, to elemental perception, to multimodal perceptions, integrated with a sense of self. At the highest levels, consciousness encompasses an individual's awareness of his or her internal state and external world, integrated with a comprehensive sense of self, linked to a perspective of past and future. One such hierarchy (Block, 1996; Young, 1998) includes the terms *crude consciousness, phenomenal consciousness* and *access consciousness.* Crude consciousness refers to alertness and wakefulness but does not imply awareness of self or the environment. Phenomenal consciousness is the basic registration of external and internal phenomena, perception at the simplest levels, not necessarily at a level of awareness apparent to the person. Access consciousness includes external and self awareness; it is awareness at a level available for directing attention, making decisions and producing action. Damasio (1999) argues that awareness of self and awareness of objects in the environment are neurobiologically intertwined. He proposes two levels of awareness of self with respect to objects, referred to as *core* and *extended consciousness.* Core consciousness provides the individual with a sense of self in the here and now. It is the simplest sense of self within the environment, without a sense of past or future, and without any requirement for memory or linguistic capacity. (Core consciousness is present in lower animals.) Extended consciousness, which itself has many gradations, refers to an elaborated sense of self in the world, within the context of an individual's history and future.

The challenge of defining consciousness is compounded further by the property of subjectivity, which has been denoted, the "hard problem" of consciousness (Chalmers, 1996). It is an issue not only in how the brain forms a sense of self but that one's consciousness is an entirely personal representation, one that cannot be fully objectified. It is accessible only through report of that person, analogy to one's own experience or inference based on behavior. This lack of an objective probe of consciousness creates one of the main challenges for clinicians who assess patients with severely impaired consciousness.

Another issue challenging the definition of consciousness is that unconscious mental operations normally occur in persons in fully conscious states. This includes cognitive operations performed at levels apart from explicit conscious awareness. Examples include priming effects on memory retrieval (Schacter,1990; Tulving & Schacter, 1990), procedural learning (Cohen & Squire, 1980) and "covert" recognition in patients with prosopagnosia (Farah et al, 1997). This also raises the question whether such nonconscious mental operations can occur at all or at some level in patients who are not fully consciousness.

The Challenge of Defining Impaired Consciousness

Assessment of impaired consciousness and accurate diagnosis is confounded by several problems. One problem concerns applying distinct labels to what is probably a continuous progression of impaired consciousness from coma to VS to MCS to confusional state to higher levels of cognitive functioning with impairment in conscious awareness. Clinicians must recognize that the boundaries between conditions may be somewhat arbitrary.

A second inherent challenge of assessment and diagnosis is that judgments concerning the presence or absence of consciousness are based on indirect evidence. Plum and Posner (1980) acknowledged this dilemma nearly two decades ago noting that, “The limits of consciousness are hard to define satisfactorily and quantitatively and we can only infer the self-awareness of others by their appearance and their acts (p. 3).” There is currently no specific biological probe for consciousness and the assessment of conscious awareness is necessarily indirect. Functional neuroimaging provides another window on the nature of consciousness and disorders of consciousness, albeit still indirect. Assessment of level of consciousness relies primarily on behavioral observation but behavior is often non-specific. The same behavior (e.g., smiling) may reflect reflexive, involuntary or intentional activity.

Cognitive awareness or conscious intent may be difficult to interpret when responses are extremely inconsistent or simple. There is an inverse relationship between the dimensions of *complexity* and *consistency* when judging whether behavior is evidence of consciousness. When a behavior is more complex, such as a verbalization, fewer instances of the response are sufficient to diagnose consciousness. When a behavior is less complex, such as a finger movement, a greater number of occurrences are necessary to establish a link to stimulus awareness or conscious intention.

Another challenge occurs in patients with limited capacity to respond because of profound motor impairment. Whether patients’ lack of cognitive behavioral responses are the result of impaired consciousness (VS, or MCS) or impaired motor responsiveness (locked-in syndrome), or some combination of these is a frequent problem that challenges diagnostic assessment.

A related confound in diagnostic assessment is whether the absence or reduction in cognitive responsiveness is the result of reduced drive, intention and initiation, or reduced cognitive awareness, or both. Akinetic mutism is a syndrome in which the main problem is a severe impairment in drive to initiate motor behavior and speech (see below).

A further challenge involves the issue of temporal flux. Recovery from unconsciousness may not be a smooth linear transition. Patients may demonstrate variability, day to day, or even moment to moment, in their capacity to demonstrate behaviors consistent with conscious awareness, especially during the transition period between consciousness and unconsciousness.

Another confound is an unusual phenomenon of patients who may have an isolated modules of cortically mediated activity producing behavior that appears to involve some level consciousness (Schiff et al., 1999). The behaviors involve stereotypical fragments of more complex, organized behavior that typically requires some significant cortical integration, however, these patients do not demonstrate any other signs of conscious behavior. The behaviors usually occur independently, without any apparent environmental contingency. (Dr. Schiff will be discussing this phenomenon in his presentation.)

While these challenges represent significant obstacles to accurate diagnosis of impaired states of consciousness, they support importance of systematic assessment and clear definitions and criteria for diagnosing these conditions of impaired consciousness. They also suggest some furtive directions for research. For instance, functional neuroimaging has just begun to provide insights into brain activity in patients with severe impairments of consciousness and will likely contribute significantly to the study of consciousness in the future. (See Dr. Schiff's syllabus.) It is also essential that terminology and diagnostic criteria be standardized to facilitate comparison of results across studies.

The Minimally Conscious State (MCS) – Definition and Clinical Criteria

The *minimally conscious state* is defined as "a condition of severely altered consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated" (Giacino et al., 2002).

The diagnostic criteria for *minimally conscious state* include limited but clearly discernible evidence of self or environmental awareness demonstrated on a reproducible or sustained basis by one or more of the following behaviors (Giacino et al., 2002):

- Simple command-following
- Gestural or verbal "yes/no" responses (regardless of accuracy)
- Intelligible verbalization
- Purposeful behavior, including movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not due to reflexive activity.

  Any of the following behavioral examples provide sufficient evidence for 'purposeful behavior.' This list is not meant to be exhaustive:

  a. Smiling or crying in response to the linguistic or visual content of emotional but not neutral topics or stimuli;
  b. Vocalizations or gestures that occur in direct response to the linguistic content of questions;
  c. Reaching for objects that demonstrates a clear relationship between object location and direction of reach;
  d. Touching or holding objects in a manner that accommodates the size and shape of the object;
  e. Pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli.

The complete definition must include criteria for the upper boundary of the condition, distinguishing minimally conscious state from higher levels of consciousness. This clinical boundary is somewhat arbitrary since emergence from MCS to higher levels of consciousness is a continuous process. There is no individual dimension that easily demarcates minimal from higher levels of consciousness. This problem points out the difficulty in defining all of these clinical states, trying to apply distinct clinical borders to a continuous process of recovery of arousal and cognition. Nevertheless, the Aspen Workgroup proposed the following clinical criteria for emergence from the minimally conscious state (Giacino et al, 2002). One or both of the following should be present:

- functional interactive communication (at least, ability to answer 6 out of 6 basic yes/no questions on 2 separate occasions regarding personal or environmental orientation [e.g., Are you sitting down?] using verbalization, writing, signaling or augmentative communication devices) or,
- functional use of objects (demonstrating the ability to appropriately use 2 different objects on 2 consecutive evaluations [e.g., bringing comb to head or pencil to paper]).

A patient's ability to communicate or use objects may be affected by loss of certain capacities such as language and praxis in a person who is otherwise fully conscious. The ability to communicate or manipulate objects may also be constrained by impairments in speech or motor abilities. In such cases, evaluation of communication and object use should be tailored to the person's preserved motor abilities, or enhanced by compensatory strategies or augmentative devices.

Prevalence of MCS

The prevalence of MCS has not been adequately investigated because this condition has only recently been defined. Strauss et al. (2000) identified 5,075 pediatric patients through the California Department of Developmental Services who were in VS or MCS. Patients were diagnosed using operational definitions based on a 261-item inventory of demographic, behavioral and cognitive data included in the state database. Of the patients studied, 11% (n = 564) were in VS and 89% (n = 4,511) were in MCS. The authors concluded that these data suggest there are between 112,000 and 280,000 adult and pediatric patients in MCS, assuming the ratio of VS to MCS patients noted in this study was similar to the general U.S. population. If accurate, these findings indicate that the prevalence of MCS in this country is eight times higher than VS (current estimates of VS = 14,000 – 35,000, Multi-Society Task Force, 1994).

Impaired Consciousness – Related Clinical Conditions

Coma (Unarousable unconsciousness)

Coma is a state of unconsciousness without the capacity for arousal (Plum & Posner, 1980). Patients in coma lack any sign of spontaneous or stimulus induced arousal. There are no purposeful movements and no signs of consciousness awareness. When occurring as a result of acquired brain damage (e.g., traumatic brain injury or anoxic brain injury), coma is an acute or subacute condition that usually evolves to the vegetative state or higher level of consciousness within 2 to 4 weeks in patients who survive (Plum & Posner, 1980; Multisociety Task Force on PVS, 1994).

Other terms are used to describe disorders of arousability and wakefulness, including *somnolence, obtundation and stupor*. These terms do not define levels of consciousness. They simply describe the patient's state of arousal at the time and are not definitive with regard to the capacity for conscious awareness. They are not interchangeable with the terms that define disorders of consciousness.

Vegetative State (Arousable unconsiousness)

The vegetative state is a condition in which there are no signs of conscious awareness but there is return of the capacity for spontaneous or stimulus-induced arousal and apparent sleep-wake cycles. There is complete or partial preservation of brainstem and hypothalamic functions. The condition may be part of the evolving course of a disorder from coma to vegetative state to higher levels of consciousness, such as the *minimally conscious state* and *confusional state*; or the end stage of a deteriorating disorder such as dementia (Volicer et al., 1997); or as a prolonged or permanent condition (Multisociety Task Force on PVS, 1994). The Multisociety Task Force on PVS (1994) proposed the term *permanent vegetative state* in cases where the probability of recovery from unconsciousness is extremely low (12 months for patients with traumatic brain injury and 3 months for patients with non-traumatic brain injury). The use of the term permanent remains controversial since there are occasional reports of patients who recover consciousness after these cutoffs (Childs & Mercer, 1996). The Task Force also proposed use of the term *persistent* vegetative state when the condition lasts greater than one month. This term is even more controversial and confusing because it has been used in a variety of ways, at different intervals post onset or sometimes implying permanence. The term *persistent vegetative state* should probably be avoided because of these ambiguities. Instead, the time from onset might be specified after the designation *vegetative state* to indicate the level of chronicity, as recommended by the Aspen Workgroup on Vegetative and Minimally Conscious States (Giacino et al., 1997).

The diagnostic criteria for vegetative state include all of the following (Multisociety Task Force on PVS, 1994):

- No evidence of awareness of self or environment
- No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli
- No evidence of language comprehension or expression
- Intermittent wakefulness manifested by the presence of sleep-wake cycles
- Sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical and nursing care
- Bowel and bladder incontinence
- Variably preserved cranial-nerve reflexes and spinal reflexes

Patients in vegetative states may move in a nonpurposeful manner. Smiling, grimacing, tearing, grunting, moaning may occur but without any apparent contingency with external or internal stimuli. Patients in the vegetative state generally do not track or fixate on objects, a capacity requiring some preservation of the cortical-subcortical visual network. Often, fixation and sustained visual pursuit are early signs of the transition to low levels of conscious awareness, such as the minimally conscious state. Giacino and Kalmar found that visual tracking did occur in as many as 20% of patients who otherwise fit the criteria for vegetative state (Giacino & Kalmar, 1997).

(Table 1 summarizes the clinical features of coma, VS and MCS [Giacino et al, 1997].)

Table 1: Comparison of clinical features of coma, VS and MCS (Giacino et al, 1997)

Diagnosis	Arousal	Awareness	Communication
Coma	Eyes do not open spontaneously or in response to stimulation	No evidence of perception, communication ability, or purposeful motor activity (e.g. command following)	No evidence of yes/no responses, verbalization, or gesture
VS	Eyes open spontaneously; sleep-wake cycle resumes; arousal often sluggish, poorly sustained but may be normal	No evidence of perception, communication ability, or purposeful motor activity	No evidence of yes/no responses, verbalization, or gesture
MCS	Eyes open spontaneously; sleep-wake cycles; arousal level ranges from obtunded to normal	Reproducible but inconsistent evidence of perception, communication ability, or purposeful motor activity; visual tracking often intact	Ranges from none to unreliable and inconsistent yes/no responses, verbalization and gesture

Acute Confusional State

Patients whose condition progresses to levels beyond what has been defined as the upper boundary of MCS usually enter a condition of greater cognitive awareness, more consistent responsiveness, but significant global cognitive dysfunction. In many cases the condition may be termed *acute confusional state*. Acute confusional state is a condition of global cognitive impairment primarily related to a deficit in attention (Mesulam MM, 2000; Lipowski, 1990). *Delirium* is another commonly used term for this condition. Abilities to focus, sustain, select and shift attention are compromised, and the coherence of perception and thought may be lost because of distractibility and mental intrusions. Patients in confusional states are usually disoriented, have difficulty sustaining mental activity, have disrupted sleep-wake cycles and have heightened or reduced levels of psychomotor activity. Confusion compromises all cognitive domains to variable extents, in large part because of the disruption of attention. Patients in confusional states are frequently confabulatory or delusional, and they may experience auditory, visual or tactile hallucinations. Perseveration and impersistence of thought and movement are other common signs. Emotion, behavior, drive and motor activity may range from a hypokinetic, apathetic, amotivational syndrome (abulia) to a hyperkinetic, agitated, impulsive, irritable, combative syndrome. Patients may display one or the other of these extremes, or may shift between syndromes as their conditions evolve, or even in the course of a day.

Acute confusional states may be a self-limited problem related to a particular neurological insult, such as a seizure or a toxic/metabolic disturbance, or may be part of the evolving natural history of a disorder such as traumatic brain injury. When part of the natural history of a disorder, acute confusional states may be a transitional stage between unconsciousness, minimal consciousness and higher levels of consciousness and cognitive functioning. Confusional states generally resolve in hours to weeks, but some patients may develop more persistent attentional and global cognitive disturbance. When chronic, other diagnostic labels, such as dementia, may be used.

Other conditions
There are a number of related neurological conditions and terms that overlap with, or must be distinguished from, the conditions defined above.

<u>Akinetic Mutism:</u> Originally described by Cairns (1941), this refers to a condition of wakefulness with an absence or paucity of speech and spontaneous movement. There is usually some evidence of conscious behavior in these patients but these behaviors are inconsistent, incomplete and usually ineffective. It is usually the drive or intent to speak or move that is severely compromised in these patients. The syndrome may be incomplete or fluctuating; some patients display varying levels of speech, movement and interaction.

A number of clinical and pathological variations of this condition have been described. In general, akinetic mutism involves bilateral damage to reticular-cortical or limbic-cortical connections in the central neuraxis, from paramedian reticular areas of the midbrain and diencephalon to basal or medial frontal areas (Plum & Posner, 1980). Damage to dopaminergic projections may be key and the condition has been partially reversed using dopaminergic agents (Anderson, 1992).

Most patients with this condition will fit the diagnostic criteria of MCS. There are some who may not, highlighting the possible discrepancy between cognitive awareness (consciousness) and the drive to move and speak (responsiveness). There may be a spectrum of this condition ranging from those with primarily motor initiation deficits and those with both motor and cognitive deficits.

<u>Dementia:</u> This term refers to a persistent or progressive impairment of intellectual function involving a number of cognitive spheres. It is a general term that may or may not imply a compromise in consciousness. Sometimes consciousness is compromised in later stages of progressive dementias. Therefore, patients with chronic impairments of consciousness may be considered demented but not all patients with dementia have impaired consciousness.

Brain death: This is an irreversible condition of complete absence of brain function, including brain-stem function. Cranial nerve function and brainstem reflexes are absent. There may be some preservation of spinal cord reflex activity. Respirations cease without external ventilator support, though the heart may continue to beat. There are prescribed criteria for diagnosing brain death, including flat line EEG or absence of metabolic activity on PET scanning, or excluding confounds such as hypothermia and CNS depressants (Beecher, 1968).

Locked-in syndrome: This is a condition of loss of voluntary motor control in the setting of preserved consciousness. The classic syndrome involves damage to corticospinal and corticobulbar pathways in the *basis pontis*. Other conditions that cause bilateral profound damage to these pathways or diffuse compromise to peripheral nerves (e.g., Guillain-Barre) or neuromuscular junction (e.g. neuromuscular blocking agents) can cause the syndrome.

It is important to distinguish impairments of consciousness from locked-in syndrome since classical locked-in syndrome implies fully preserved consciousness. It should be recognized, however, that many patients in vegetative or minimally conscious states have profound loss of motor abilities because of concomitant damage to motor control areas. It may be difficult to demonstrate conscious behavior as it emerges in these patients because of limited motor output capabilities. Clinicians must be vigilant for signs of cognitive awareness in patients with very limited motor response capabilities, since consciousness may emerge, masked by the loss of motor ability.

Prognosis

Outcome of Vegetative State

The Multi-Society Task Force on PVS (1994) reviewed the available outcome data for patients in the vegetative state. They considered two outcomes: regaining consciousness and functional outcome based on Glasgow Outcome Scale (Jennett & Bond, 1975). Data were analyzed on 434 adults and 106 children with traumatic brain injury, and 169 adults and 45 children with nontraumatic brain injury – primarily patients with anoxic brain injury and stroke. Of the adults with traumatic brain injury who were unconscious at least 1 month, 33% recovered consciousness by 3 months post-injury and 52% by 1 year. If patients were still unconsciousness at 3 months, 35% regained consciousness by one year. The probability of regaining consciousness was considerably lower for adults with nontraumatic brain injuries. Of those unconscious for 1 month, only 11% recovered consciousness at 3 months and 15% at six months. There were no additional recoveries after 6 months for those with nontraumatic injuries. Children fared only a little better. Up to 62% regained consciousness at one year after traumatic brain injury; after nontraumatic injury, recovery of consciousness was observed largely in the first 3 months (11%), with a very small percentage (2%) regaining consciousness between 6 and 12 months. (See table 2 for a summary of these outcome data.) The Task Force concluded that prognosis for recovery of consciousness was very poor 12 months after traumatic injuries and 3 months after nontraumatic brain injury for both adults and children. They deemed that vegetative state is *permanent* if there is no sign of consciousness by these intervals after injury.

Some caution is warranted in the use of the term *permanent* vegetative state at 3 and 12 months, since the number of patients with traumatic brain injury followed after 12 months is limited and there are several reports of patients who regain consciousness after these times (Multisociety Task Force on PVS, 1994; Childs & Mercer, 1996). Although probability of recovery of consciousness is very low after these times, the chance of recovery is not absolutely lost.

The probabilities for functional outcome at 12 months, based on the Glasgow Outcome Scale, in those that regain consciousness, is summarized in table 2. Of adults who recover consciousness by 12 months after traumatic brain injury, more than 1/2 were *severely disabled*, nearly 1/3 were *moderately disabled* and a little more than 1/8 were at a *good recovery* level. After nontraumatic injury, nearly ¾ of those who regain consciousness remained severely disabled at 12 months. Children fared a little better for nontraumatic injuries in that over ½ were severely disabled and nearly ½ achieved a good recovery level. Adults over age 40 had a considerably worse prognosis, rarely better than the severe disability level of recovery.

<u>Table 2.</u> Prognosis and functional outcome for adults after prolonged unconsciousness in patients with traumatic brain injury (TBI) or nontraumatic brain injury (nonTBI). (Multi-Society Task Force on PVS, 1994) (VS = vegetative state; SD = severe disability; MD = moderate disability; GR = good recovery)

•Unconscious at least 1 month:
–TBI: 33% death, 15% VS, 28% SD, 17% MD, 7% GR
–nonTBI: 53% death, 32% VS, 11% SD, 3% MD, 1% GR
•Unconscious at least 3 months:
–TBI: 35% death, 30% VS, 19% SD, 16% MD or GR
–nonTBI: 46% death, 47% VS, 6% SD, 1% MD or GR
•Unconscious at least 6 months:
–TBI: 32% death, 52% VS, 12% SD, 4% MD or GR
–nonTBI: 28% death, 72% VS, 0% SD, 0% MD or GR

Mortality rates were relatively high for patients in vegetative states at least 1 month, 82% at 3 years, and 95% at five years (Multisociety Task Force on PVS, 1994). These figures do not consider somewhat better life expectancy in those that survive the first year and do not account for recent improvements in survival with better medical care.

Neuroimaging and electrophysiologic studies may add some prognostic information. Kamplf and colleagues (1998) found that location of brain lesions after trauma was a better predictor of recovery from prolonged unconsciousness than Glasgow Coma Scale scores, age and papillary abnormalities. Patients who did not recover consciousness by 12 months had a significantly higher frequency of corpus callosum, corona radiata and dosolateral brainstem lesion than those that did regain consciousness. Somatosensory evoked potential studies may be useful in predicting outcome of vegetative state after anoxic brain injury. Absence of the N20 potential in the presence of the earlier N14 potential is very poor prognostic sign for recovery of consciousness (Zegers de Beryl & Brunko, 1986).

Outcome of Minimally Conscious State

There is very little specific information about the prognosis of the MCS. Most of the information contrasts recovery of patients in MCS with patients in VS. Rappaport and coworkers (1992) reported improvement in 25% of a small group of patients with impaired consciousness followed over a 4-month period. Only those in MCS (referred to as "near-coma") improved; none in VS improved in the follow-up period.

Giacino & Kalmar (1997) compared outcomes of patients in VS versus MCS. In this study 55 patients in VS were compared to 49 patients in MCS when they were first evaluated an average of 9.6 weeks post-injury. Causes of injury were traumatic (n=70) and non-traumatic (n=34) (mostly anoxic brain injury and stroke). Using the Disability Rating Scale as the outcome measure at 1,3,6, and 12 months post-injury, they reported the following findings:

1. Patients initially in MCS fared better than those initially in VS, the differences becoming progressively more apparent at 3, 6 and 12 months post-injury.
2. The probability of a more favorable outcome (moderate or no disability) by one year was much greater for the MCS group (38%) than the VS group (2%) and only occurred in those patients with traumatic brain injury.
3. 43% of the MCS group remained severely disabled or worse (1/10 of the non-traumatic MCS group was vegetative and 2/10 died) at 12 months.
4. So-called "borderzone" clinical signs (visual tracking, motor agitation) were much more prevalent among patients in MCS than those in VS. 73% of patients in VS who displayed tracking recovered consciousness, whereas 45% without tracking recovered consciousness.

A cohort of patients with MCS and VS were followed as part of a multicenter study of patients with prolonged impairments of consciousness. A subgroup of 96 patients with TBI were analyzed with regard to predictors of outcome (Katz et al., 2002; Whyte et al., 1999). Predictor variables included initial Disability Rating Scale scores (DRS) (Rappaport et al, 1982) at rehabilitation admission, change in DRS scores in the first 2 weeks, Glasgow Coma Score at injury, categorization of traumatic pathology (diffuse axonal injury, focal parenchymal lesion, epidural, subdural, subarachnoid hemorrhage), location of focal injury (lobar, brainstem, diencephalic), secondary processes (herniation, intracranial hypertension, hypoxia), CNS active medications during the first 4 weeks of rehabilitation admission. The best predictors of outcome at 4 months post-injury were the initial DRS score, the early (2 week) rate of improvement in DRS, and the time from injury to rehabilitation admission, predicting 54% of the variance, using the DRS as the outcome measure. Of the CNS active medications, amantadine had a significant positive effect on outcome. Neuropathological variables did not add to the prediction model.

Neuropathological Studies and outcome of VS and MCS

Recent neuropathological studies analyzing patients who remained in VS or MCS until death add insights to correlates of location of brain damage and outcome in these conditions.

Adams and colleagues (2000) analyzed the brains of 35 patients who remained in VS until death following TBI. The most common structural abnormality was diffuse axonal injury (grades 2 and 3), occurring in 71% of cases. DAI was characterized by focal lesions in the corpus callosum or rostral brain stem and was associated with moderate to severe ischemic damage involving the thalamus (80%) and arterial watershed areas (43%). Only 14% of cases had focal brain stem lesions not accounted for by DAI. From these data, the authors hypothesized that late recovery from traumatic VS could be accounted for by gradual restoration of axonal function in those cases with sufficient preservation of the thalamus. The authors also studied 14 cases of non-traumatic injury. The majority of cases (64%) had diffuse neocortical ischemic damage. Thalamic abnormalities and profound damage to the subcortical white matter and/or to the major thalamic relay nuclei were noted in every case. Any remaining structurally intact cortex appeared to be functionally disconnected from the thalamic nuclei and inter-cortical connectivity was severely compromised. The loss of thalamocortical connection may be the most important cause of permanent absence of cognitive activity in cases of VS.

In a follow-up study, Jennett and coworkers (2001) evaluated neuropathologic differences in traumatically-induced VS and MCS. The same group of VS subjects reported in Adams et al. (2000) was compared to 30 subjects, all of whom were rated as severely disabled (SD) on the Glasgow Outcome Scale until death. The SD group was sub-categorized further into subjects who were mobile (n = 9), bed-bound (n = 9) or in MCS (n = 12). The authors hypothesized that the structural lesions in the SD group would be similar to those in the VS group but less severe. Findings unexpectedly did not support this hypothesis. In 50% of the SD cases, there was no evidence of grade 2 or 3 DAI and no indication of thalamic damage. This was in marked contrast to the VS group, all of whom had moderate to severe DAI and thalamic lesions. In the MCS cases, grade 2 or 3 DAI was more frequent than in the SD cases (42 versus 22%) but considerably less frequent than in the VS cases (71%). Thalamic lesions were also notably less prevalent in MCS (50%) relative to VS (80%).

The neuropathological findings in VS and MCS described above appear to be consistent with the results of prior studies comparing clinical outcome between these conditions. The preservation of consciousness and more favorable trajectory of recovery noted in MCS is likely attributable to sufficient sparing of cortico-cortical and cortico-thalamic connections.

Impaired Consciousness in the Natural History of Recovery after Brain Injury

Coma, vegetative state, minimally conscious state and acute confusional state should be viewed as a part of the natural history of diffuse and multifocal brain injury. The majority of patients with diffuse brain injury (traumatic and non-traumatic) pass through a series of stages that are qualitatively similar across a wide range of severity. Several scales, such as the Rancho Los Amigos Levels of Cognitive Functioning and Braintree Neurological Stages of Recovery, have been developed to track these transitions (see table 3).

Table 3. Scales to track progression through stages of impaired consciousness – Rancho Los Amigos Scale (Hagen et al., 1972) and Braintree Stages of Neurological Recovery (Katz, 1992; Katz & Mills, 1999; Alexander, 1982).

Rancho Los Amigos Levels of Cognitive Functioning

I. No Response
II. Generalized Responses
III. Localized Responses
IV. Confused - Agitated
V. Confused - Inappropriate
VI. Confused - Appropriate
VII. Automatic - Appropriate
VIII. Purposeful and Appropriate

Braintree Stages of Neurologic Recovery (Diffuse Brain Injury)

1. Coma / unarousable unconsciousness: unresponsive, eyes closed

2. Vegetative state / arousable unconsciousness: no cognitive responsiveness, gross wakefulness, sleep-wake cycles

3. Minimally conscious state: inconsistent response to commands, inconsistent but definite signs of purposeful behavior

4. Confusional state: recovered communication, amnesic (posttraumatic amnesia [PTA]), severe attentional deficits, agitated, hypoaroused or labile behavior

5. Post-confusional / evolving independence: resolution PTA, cognitive improvement, achieving independence in daily self care, improving social interaction; developing independence at home

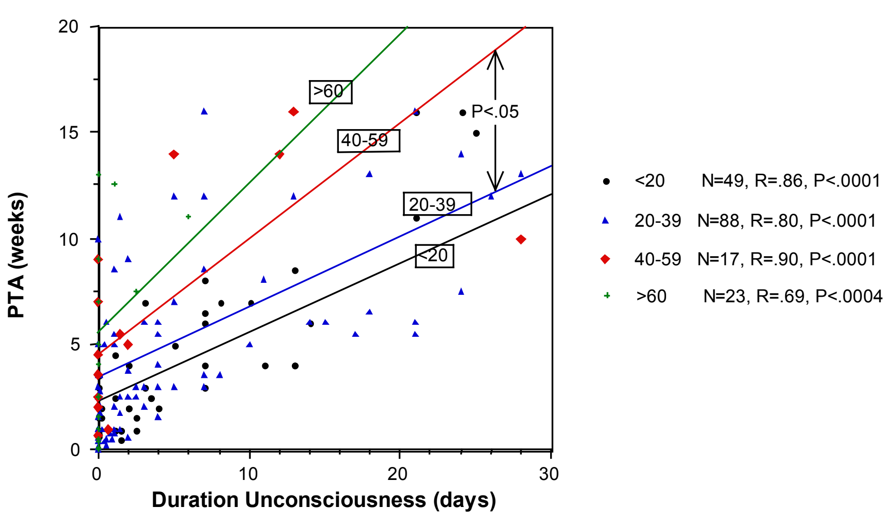
6. Social competence / community reentry: safety and independence in the home, recovering cognitive abilities, goal directed behaviors, social skills, personality; developing independence in community; returning to academic or vocational pursuits

The Rancho Los Amigos Levels of Cognitive Functioning (RLA) (Hagen, 1972) is commonly used in rehabilitation populations, especially for patients with traumatic brain injury. The first three levels of this 8 level scale describe patients in coma (RLA I – no response), vegetative state (RLA II – generalized responses) and the transition between vegetative and minimally conscious states (RLA III – localized responses).

The Braintree Neurological Stages of Recovery is a similar scale used to describe stages of recovery after diffuse brain injury but incorporates some of the more familiar neurological nomenclature (Katz, 1992, 1997, Katz and Alexander, 1994; Alexander, 1982). The duration of these stages and severity of impairments vary in proportion to injury severity (Katz, 1997; Katz & Alexander, 1994). Most patients with brain injury severe enough to cause unconsciousness, probably progress through stages of unconsciousness, with eyes closed (*coma*), to unconsciousness with eyes open (*vegetative state*), to a stage of inconsistent, erratic responsiveness (*minimally conscious state*). Once consciousness is clearly established, patients enter a stage of impaired attention and anterograde amnesia (e.g., post-traumatic amnesia) (*confusional state*) followed by a post-confusion phase of recovery.

In patients with diffuse traumatic brain injury (diffuse axonal injury) there is a predictable, proportional relationship between the duration of unconsciousness (coma and vegetative state) and the duration of the confusional state (post-traumatic amnesia) (Katz & Alexander, 1994; Katz et al, 1999). The relationship can be described by a simple regression model explaining over ½ of the variance in predicting the duration of post-traumatic amnesia and confusion: duration of PTA (weeks) = 0.4 X duration of unconsiousness (days) + 3.6. In addition to the duration of unconsciousness, age had a significant effect on prolonging the duration of PTA/confusion (see fig. 1).

Fig. 1. Relationship duration of unconsciousness to PTA at different age groups



In patients with very severe damage, recovery may stall at one or another stage (e.g., "*permanent" vegetative state or minimally conscious state*). Patients with less severe injuries may transition through the early stages quickly and discrete stages may not be clinically apparent. It remains to be established what proportion of patients recovering from unconsciousness at different severities of injury evolve through discernible coma, vegetative and minimally conscious stages.

Viewed in this way, the transition from unconsciousness to consciousness is a continuum without distinct boundaries. As the transition progresses, and cortical function resumes, the consistency and complexity of behavior increases. The first signs of the transition may be an increase in alertness and spontaneous movement with lower levels of stimulation, such as the arrival of the examiner (Wilson et al., 1996). At the borderzone, behaviors such as tracking, emotional expressions and non-stereotyped motor sequences resume, heralding higher level cognitive behaviors (Ansell, 1995; Multisociety Task Force on PVS, 1994; Giacino & Kalmar, 1997). A small number of patients will recover these “borderzone” behaviors without resuming any other cognitive behavior, such as following commands (Giacino & Kalmar, 1997).

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