

Current controversies in states of chronic unconsciousness



James L. Bernat, MD

Address correspondence and reprint requests to Dr. James L. Bernat, Neurology Department, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756
bernat@dartmouth.edu

Neurology® Clinical Practice
2010;75(Suppl 1):S33-S38

Coma resulting from brain injury or illness usually is a transient state. Within a few weeks, patients in coma either recover awareness, die, or evolve to an eyes-open state of impaired responsiveness such as the vegetative or minimally conscious state. These disorders of consciousness can be transient stages during spontaneous recovery from coma or can become chronic, static conditions. Recent fMRI studies raise questions about the accuracy of accepted clinical diagnostic criteria and prognostic models of these disorders that have far-reaching medical practice and ethical implications.

A 21-year-old woman lost control of her car and struck a bridge abutment. She sustained a severe traumatic brain injury (TBI) with subdural, subarachnoid, and intracerebral hemorrhages that was complicated by intracranial hypertension and generalized seizures. When examined in the neurorehabilitation center 6 months later, she was in a vegetative state with eyes-open wakefulness but without awareness of herself or her environment, no psychological responsiveness, and marked spasticity with little movement of her limbs. Her eyes were open and moving when she was awake and were closed when she was asleep. Brain CT scan showed bilateral thalamic and multifocal cortical areas of encephalomalacia with ex vacuo hydrocephalus. Her EEG had an irregular 4-Hz background with intermittent sharp waves over the right hemisphere.

Six months later, her parents reported that she had become responsive. The examiner could, at times, get her to follow a \$20 bill with her eyes and to reach toward it but she followed no commands. Her pupillary light reflexes were normal and she had roving, full eye movements. Most of the time, examiners and staff members could elicit no responsiveness. She breathed spontaneously through a tracheostomy tube and was fed and hydrated by a gastrostomy tube. She required daily physical therapy to prevent contractures that had developed in all her limbs. Repeat brain imaging and EEG were unchanged. Her parents asked if she could undergo fMRI assessment which they discovered on an Internet search might prove that she was aware and could improve.

DIAGNOSTIC ISSUES The vegetative state (VS) and minimally conscious state (MCS) are the principal clinical syndromes of patients with chronically disordered consciousness. As syndromes, they encompass a spectrum of severity and can be the consequence of a variety of brain injuries and illnesses.¹ Categorizing patients with disorders of consciousness into the correct diagnostic syndrome is essential, but the prognosis of each patient depends mostly on the cause and extent of the brain damage producing the syndrome.

The VS has been epitomized as “wakefulness without awareness” because the brainstem reticular system responsible for alertness and wakefulness remains intact but the thalamocortical systems responsible for awareness have been damaged. The VS is best conceptualized as a disconnection syndrome between the thalami and the cortex resulting from 1) bilateral thalamic damage; 2) diffuse cortical damage, especially involving the precuneus; or 3) damage to the white matter tracts connecting the thalami and cortex. The principal causes of VS are 1) TBI, which can cause damage by all 3 mechanisms, but especially by white matter tract damage from severe diffuse axonal injury because of rotational brain trauma; 2) hypoxic-ischemic neuronal damage to the

From the Departments of Neurology and Medicine, Dartmouth Medical School, Hanover, NH.

Disclosure: Author disclosures are provided at the end of the article.

Table 1 Criteria for diagnosing a vegetative state

Unaware of self and environment
No interaction with others
No sustained, reproducible, or purposeful voluntary behavioral response to visual, auditory, tactile, or noxious stimuli
No language comprehension or expression
No blink to visual threat
Present sleep-wake cycles
Preserved autonomic and hypothalamic function to survive for long intervals with medical/nursing care
Preserved cranial nerve reflexes
Bowel and bladder incontinence

Modified, with permission, from: Bernat JL. *Ethical Issues in Neurology*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:289.

cortex and thalami during cardiopulmonary arrest; and 3) brain infarction or hemorrhage with thalamo-cortical damage.¹

The vegetative state has been epitomized as “wakefulness without awareness”

The diagnostic criteria for the VS are listed in table 1 and the potential behavioral repertoire of the patient in VS is listed in table 2. That most of the clinical diagnostic criteria are delineated as negatives stipulating those functions patients in VS lack permits false-positive determinations. Several studies of the diagnostic accuracy of VS using these criteria found a disturbingly high false-positive rate of 40% in which patients with MCS were erroneously diagnosed in VS.² Examiners must pay special attention to any evidence for awareness and not diagnose VS if such evidence is present.

The MCS is a related clinical syndrome of profound unresponsiveness but one that features nominal and intermittent evidence for awareness. Patients may develop MCS from the same disorders that produce VS. A common evolution after diffuse brain injury is coma progressing to the VS and then to the MCS. Like patients in VS, patients in MCS have generally intact brainstem function but they tend to have greater preservation of thalamocortical function than patient in VS. The diagnostic criteria for MCS are listed in table 3 and the potential behavioral repertoire of the patient in MCS is listed in table 4.

There is an irreducible biologic limitation to knowing the conscious life of another person. We can determine a patient’s awareness only by interacting with the patient and, based on the patient’s responses to stimuli, inferring judgments about his or

Table 2 Potential behavioral repertoire of patients in a vegetative state

Sleep-wake cycles with eyes closed, then open
Spontaneous breathing
Spontaneous blinking and roving eye movements
Nystagmus
Vocalization of sounds but no words
Brief, unsustained visual pursuit
Grimacing to pain, changing facial expressions
Yawning; chewing jaw movements
Swallowing of saliva
Nonpurposeful limb movements; arching of back; decorticate limb posturing
Flexion withdrawal from noxious stimuli
Brief movements of head or eyes toward sound or movement without apparent localization or fixation
Auditory startle
Startle myoclonus
Sleep-related erections

Modified, with permission, from: Bernat JL. *Ethical Issues in Neurology*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:289.

her conscious life. Therefore, there is no objective gold standard test for detection of awareness; it remains solely determined by behavioral observation.³ Yet it is challenging to discern behavioral signs of awareness in some poorly responsive patients because their repertoire of potential behaviors is limited and present only inconsistently. Specialized neurobehavioral assessment tools to assess poorly responsive patients have been formulated and validated to sensitively identify subtle behavioral evidence of awareness.⁴ Family members and staff members should be interviewed because often they are the first to note subtle signs of emerging awareness in those patients in VS who evolve to MCS.

Table 3 Criteria for diagnosing a minimally conscious state

Globally impaired responsiveness
Limited but discernible evidence of awareness of self and environment as demonstrated by the presence of 1 or more of the following behaviors:
Following simple commands
Gestural or verbal responses to yes/no questions
Intelligible verbalization
Purposeful behavior: movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not simply reflexive movements (see table 4)

Modified, with permission, from: Bernat JL. *Ethical Issues in Neurology*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:291.

Table 4 Potential behavioral repertoire of patients in a minimally conscious state

Follow simple commands
Gesture yes/no answers
Verbalize intelligibly
Vocalize or gesture in direct response to a question's linguistic content
Reach for objects demonstrating a clear relationship between object location and direction of reach
Touch and hold objects in a manner that accommodates the size and shape of the object
Sustain visual pursuit of moving stimuli
Smile or cry appropriately to linguistic or visual content of emotional but not of affectively neutral topics or stimuli

Modified, with permission, from: Bernat JL. *Ethical Issues in Neurology*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:291.

CONTRIBUTION OF FMRI Early functional imaging studies of patients in VS with PET showed a markedly diminished baseline state of neuronal metabolism similar to that recorded in normal subjects in the deepest plane of general anesthesia. Subsequent PET and fMRI studies of the evoked effects on regional cerebral blood flow by various sensory stimuli showed that while primary cortical areas could be activated, the higher-order widespread distributed cortical networks believed to be necessary for awareness could not. These studies showed that patients in VS lack the capacity for any stimuli to activate higher-order multimodal cortices, especially the precuneus, which comprise the integrated, distributed neural networks believed to be necessary for conscious awareness. Further, when patients in VS recover awareness, the resumption of functioning of their damaged thalamocortical circuits can be demonstrated by fMRI.

Recent fMRI studies employing ideational paradigms have challenged our understanding of VS and may alter the accepted correlation between clinical and neuroimaging findings. In 2006, Owen and colleagues⁵ reported surprising fMRI findings on a 23-year-old woman who had been in VS for 5 months following TBI. She was given 2 ideational tasks: first, to imagine playing tennis and to think of the ball being volleyed back and forth over the net; second, to imagine walking through the rooms of her house and to think of the objects she would see. During the tennis-playing ideational task, her fMRI showed activation of the supplementary motor area. During the house tour ideational task, her fMRI showed activation of the parahippocampal gyrus, posterior parietal lobe, and lateral premotor cortex. Each of these patterns was similar in location but less in intensity to those evoked in normal aware subjects given the

same tasks. Owen and colleagues⁵ concluded that “beyond any doubt [the patient] was consciously aware of herself and her surroundings.” Six months later, she began to show clinical signs of awareness, hence had graduated to the clinical syndrome of MCS.

Earlier this year, Monti and colleagues (including Owen)⁶ at the Universities of Cambridge and Liège reported similar findings in additional cases. Of the cohort of 23 patients in VS they examined over the study interval were 4 who, by fMRI responses, had the ability to “willfully modulate” their own brain activity on command, one of whom was the patient described previously by Owen et al. All 4 patients in VS with this ability had had TBI with diffuse axonal injury; it was not observed in any patient with hypoxic-ischemic neuronal injury from cardiac arrest. The mean age of the patients was 28 years. Two were examined within 6 months of injury, 1 at 30 months, and 1 at 61 months after injury.⁶

If one assumes that the capacity for “willful modulation” of brain activity requires awareness of self (and some knowledgeable commentators remain skeptical about this claim⁷), these fMRI findings show that the clinical examination, at times, may be insensitive to the presence of awareness. If this conclusion is true, it means that elicited fMRI data can complement findings on the neurologic examination and contribute to a more accurate diagnosis.⁸ This conclusion has profound importance for the clinical assessment and humane treatment of patients believed to be in VS.

PROGNOSTIC ISSUES Determining the accurate prognosis of VS and MCS is a critical step in counseling families and determining appropriate treatment. Previous studies of prognosis in VS were limited by several factors: 1) because there were no accepted diagnostic criteria for MCS prior to 2002, some patients in MCS in those studies may have been diagnosed with VS; 2) it is more accurate to determine prognosis by the etiology of brain damage than merely by categorization in a clinical syndrome; and 3) retrospective experiential analyses of outcomes, such as that by the Multi-Society Task Force, committed the fallacy of the self-fulfilling prophecy because they included patients in their survival data who died primarily because their life-sustaining therapy was discontinued.⁹ Nevertheless, the prognostic guidelines published in 1994 by the Multi-Society Task Force on PVS have been generally accepted, showing a very low probability of recovering awareness once VS has been present for a year following TBI or for 3 months following hypoxic-ischemic neuronal injury.¹

Two recently published studies of prognosis in VS add useful data. Luauté and colleagues¹⁰ confirmed the prognostic guidelines of the Multi-Society Task Force in all the patients in VS they studied and showed that age greater than 39 years and absence of the middle-latency auditory evoked potentials were independent early predictors of poor outcome irrespective of pathogenesis. Estraneo and colleagues¹¹ found that 88% of patients in VS in their series conformed to the Multi-Society Task Force prognostic guidelines but 12% made late recoveries of awareness but only to the point of severe disability with MCS, most of whom had TBI. Because of varying pathophysiologies, prognostic indicators for MCS as a group have been difficult to establish whereas prognostic indicators in individual pathophysiologic subsets of MCS (e.g., patients in MCS from TBI) have been more reliable.⁹

Emerging fMRI data also may influence prognosis. The clinically diagnosed patient in VS reported by Owen and colleagues improved to MCS a few months after her fMRI showed evidence of her capacity to willfully modulate her brain activity. This pattern of clinical improvement also was seen in the small subset of VS cases reported by Di and colleagues¹² who showed fMRI evidence of the capacity to activate perisylvian language regions in response to hearing their own name spoken. It is therefore possible that the small subset of patients in VS demonstrating patterns of fMRI responses suggesting awareness is itself predictive of future clinical improvement. This important hypothesis requires verification with more cases before it is established.

TREATMENT ISSUES Specialized neurorehabilitation units are the optimal treatment venue for patients with chronic disorders of consciousness, at least until they are no longer improving. Patients have better functional outcomes when treated by skilled personnel who have been trained in neurorehabilitation.

The difference between patients in VS and patients in MCS in their response to stimulatory treatment is noteworthy: patients in VS rarely improve as a consequence of stimulation but patients in MCS may improve to some extent. Treatment modalities that have been studied include environmental and sensory stimuli such as sounds, smells, touch, images, and music. Pharmacologic stimuli include treatment with stimulants, levodopa, and dopamine agonists (by stimulating intact dopaminergic thalamic neurons), and selective serotonin reuptake inhibitor antidepressants. Electrical stimuli include deep brain stimulation of medial thalamic nuclei. Each of these modalities has been reported to improve functional

responsiveness in some patients in MCS though there are few controlled studies.⁴ These therapies are also widely tried in patients in VS but a meta-analysis of their outcomes showed no consistent benefits.⁴ If neurologists prescribe them for patients in VS, their families should be counseled that they are unlikely to be of benefit.

ETHICAL ISSUES The appropriate level of treatment of patients with chronic disorders of consciousness depends on their diagnosis, prognosis, and prior stated treatment values and preferences. Neurologists should assure the accuracy of the diagnosis and make an evidence-based prognosis based on published data. They should assure that their explanation of diagnosis and prognosis is not colored by their bias or values about treatment in states of disability. For example, some patients and their families may consider moderate or severe disability to be an acceptable level of outcome even if their neurologists do not.

Neurologists should strive to practice patient-centered medicine in which they respect the treatment decision made by the patient's lawful surrogate decision-maker who attempts to faithfully represent the treatment preferences of the patient. Surrogate decision-makers need to know the patient's diagnosis and prognosis, the neurologist's degree of confidence in both, and the wishes of the patient in this situation. They also need to understand the neurologist's recommended treatment plan and the reason it is recommended. In my experience, most surrogates of young patients with TBI request aggressive rehabilitative and stimulatory treatment, hoping for improvement. Conversely, in older patients in VS, surrogates are more likely to order withdrawal of life-sustaining therapy once it becomes clear that the patient will remain unconscious. Paradoxically, the emerging fMRI data may aggravate the ethical dilemma by reaching a treatment conclusion prematurely.¹³

Some investigators have reported that patterns of evoked fMRI data may be used to provide a unique channel to communicate with unresponsive patients. One of the clinically diagnosed patients in VS reported by Monti and colleagues⁶ was able to answer "yes-no" in response to questions through reproducible evoked changes in regional cerebral blood flow on fMRI. Assuming that these findings were valid, how can examiners be certain that with such rudimentary communication, patients understand the questions adequately? The risks and benefits of this means of communication should be thoughtfully studied. Decisions to discontinue life-sustaining therapy based on patient responses to questions by this technique require particular scrutiny and skepticism.

The question of suffering is relevant to ethical decision-making. Most authorities formerly agreed that the patient in VS was incapable of suffering because he or she remained unaware and incapable of experience, to the fullest extent that this capacity could be determined. This important conclusion has become less certain in light of the emerging fMRI case reports suggesting that some young patients with TBI diagnosed as in VS may have a residual capacity for some degree of awareness that cannot be elicited on neurologic examination. Everyone agrees that the patient in MCS remains capable of suffering. Appropriate palliative care must be employed for any patient with disordered consciousness for whom the surrogate reaches the decision to withhold life-sustaining therapy.

RESPONSE TO THIS CASE The patient presented here probably has graduated from VS to MCS given her intermittent ability to visually follow and reach for a presented object. Yet she remains profoundly unresponsive to most stimuli and may be unaware most of the time. Thus, the true state of her level of awareness remains unknown.

The neurologist or psychiatrist caring for the patient should explain to her parents that the fMRI paradigms reported by the press, about which they read on the Internet, remain experimental and are neither available nor recommended for current clinical usage. There are only a few medical centers that have the capacity to perform these studies, given the technological requirements for the fMRI paradigms. The case reports of fMRI responses have not been adequately validated to achieve recommendation for general clinical usage.¹⁴ They probably will come into general clinical usage in the future but not until they have been better validated with more cases to determine their true positive and negative predictive value.

The neurologist can order neurorehabilitation therapy and can offer cautious trials of treatment, including medications if they are not contraindicated by the patient's seizures. In my practice, I usually initiate amantadine or levodopa-carbidopa in the same dosage range as used for treating Parkinson disease. I also try usually to prescribe a trial of zolpidem, which has been reported to improve function in a small proportion of patients with MCS, presumably by stimulating intact thalamic neurons. Deep brain stimulation has been shown to be effective in a

single case of MCS that was selected because of the presence of intact thalamic neurons capable of being stimulated, and remains experimental.

DISCLOSURE

Dr. Bernat serves on the editorial boards of *Neurocritical Care* and *Neurology Today* and receives royalties from the publication of *Ethical Issues in Neurology, 3rd ed.* (Lippincott Williams & Wilkins, 2008) and *Palliative Care in Neurology* (Oxford University Press, 2004).

Received June 10, 2010. Accepted in final form August 30, 2010.

REFERENCES

1. Bernat JL. Chronic consciousness disorders. *Annu Rev Med* 2009;60:381–392.
2. Schnakers C, Vanhaudenhuyse A, Giacino J, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol* 2009;9:35.
3. Giacino JT, Schnakers C, Rodriguez-Moreno D, Kalmar K, Schiff N, Hirsch J. Behavioral assessment in patients with disorders of consciousness: gold standard or fool's gold? *Prog Brain Res* 2009;177:33–48.
4. Bernat JL. Chronic disorders of consciousness. *Lancet* 2006;367:1181–1192.
5. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. *Science* 2006;313:1402.
6. Monti MM, Vanhaudenhuyse A, Coleman MR, et al. Willful modulation of brain activity in disorders of consciousness. *N Engl J Med* 2010;362:579–589.
7. Ropper AH. Cogito ergo sum by MRI. *N Engl J Med* 2010;362:648–649.
8. Coleman MR, Davis MH, Rodd JM, et al. Toward the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain* 2009;132:2541–2552.
9. Bernat JL. The natural history of chronic disorders of consciousness. *Neurology* 2010;75:206–207.
10. Luaute J, Maucourt-Boulch D, Tell L, et al. Long-term outcomes of chronic minimally conscious and vegetative states. *Neurology* 2010;75:246–252.
11. Estraneo A, Moretta P, Loreto V, Lanzillo B, Santoro L, Trojano L. Late recovery after traumatic, anoxic or hemorrhagic long-lasting vegetative state. *Neurology* 2010;75:239–245.
12. Di HB, Yu SM, Weng XZ, et al. Cerebral response to patients' own name in the vegetative and minimally conscious states. *Neurology* 2007;68:895–899.
13. Wilkinson DJ, Kahane G, Horne M, Savulescu J. Functional neuroimaging and withdrawal of life-sustaining therapy from vegetative patients. *J Med Ethics* 2009;35:508–511.
14. Fins JJ, Illes J, Bernat JL, Hirsch J, Laureys S, Murphy E. Neuroimaging and disorders of consciousness: envisioning an ethical research agenda. *Am J Bioethics* 2008;8:3–12.

If you liked this article, you may be interested in. . .



Neurology

S. Silva et al. Wakefulness and loss of awareness: Brain and brainstem interaction in the vegetative state. January 26, 2010; www.neurology.org

JL Bernat. The natural history of chronic disorders of consciousness. July 20, 2010; www.neurology.org

A. Estraneo et al. Late recovery after traumatic, anoxic or hemorrhagic long-lasting vegetative state. July 20, 2010; www.neurology.org

J. Luauté J et al. Long-term outcomes of chronic minimally conscious and vegetative states. July 20, 2010; www.neurology.org



Neurology Now

Mike Smolinsky. Brain Imaging. July/August 2008; www.neurologynow.org

Gina Shaw. Making Sense of Brain Death. May/June 2010; www.neurologynow.org



Neurology Today

Richard Robinson. New Functional Imaging Study of PVS Sheds Light on Nature of Consciousness. February 4, 2010; www.neurotodayonline.com

Jamie Talan. Fanfare - and Caution - Greet Report that Patients with Consciousness Disorders Understand and Respond to Language. March 4, 2010; www.neurotodayonline.com

Lola Butcher. Should Feeding Tubes Always Be Continued in Terminal Illness? Not Necessarily, According to New Guidance from the Catholic Church. June 17, 2010; www.neurotodayonline.com

Jamie Talan. Two New Papers Offer Insight: To What Extent do People with Consciousness Disorders Recover? July 15, 2010; www.neurotodayonline.com

Neurology[®]

Current controversies in states of chronic unconsciousness

James L. Bernat

Neurology 2010;75;S33-S38

DOI 10.1212/WNL.0b013e3181fb35dd

This information is current as of November 1, 2010

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/75/18_Supplement_1/S33.full
References	This article cites 14 articles, 6 of which you can access for free at: http://n.neurology.org/content/75/18_Supplement_1/S33.full#ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://n.neurology.org/content/75/18_Supplement_1/S33.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Ethics in Neurology/Legal issues http://n.neurology.org/cgi/collection/all_ethics_in_neurology_legal_issues Coma http://n.neurology.org/cgi/collection/coma Critical care http://n.neurology.org/cgi/collection/critical_care Prognosis http://n.neurology.org/cgi/collection/prognosis
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2010 by AAN Enterprises, Inc.. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

