Chronic disorders of consciousness

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The vegetative state and the minimally conscious state are disorders of consciousness that can be acute and reversible or chronic and irreversible. Diffuse lesions of the thalami, cortical neurons, or the white-matter tracts that connect them cause the vegetative state, which is wakefulness without awareness. Functional imaging with PET and functional MRI shows activation of primary cortical areas with stimulation, but not of secondary areas or distributed neural networks that would indicate awareness. Vegetative state has a poor prognosis for recovery of awareness when present for more than a year in traumatic cases and for 3 months in non-traumatic cases. Patients in minimally conscious state are poorly responsive to stimuli, but show intermittent awareness behaviours. Indeed, findings of preliminary functional imaging studies suggest that some patients could have substantially intact awareness. The outcomes of minimally conscious state are variable. Stimulation treatments have been disappointing in vegetative state but occasionally improve minimally conscious state. Treatment decisions for patients in vegetative state or minimally conscious state should follow established ethical and legal principles and accepted practice guidelines of professional medical specialty societies.

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Chronic unconsciousness is a tragic and ironic failure of high-technology treatment to preserve or restore brain function, the primary aim of therapeutics. Management of a patient in a vegetative state or a minimally conscious state requires carefully reaching the correct diagnosis, pronouncing an evidence-based prognosis, and thoughtfully considering the medical, ethical, and legal elements of optimum treatment. In the USA, the case of Theresa Schiavo in 2005 brought many of these issues to intense public scrutiny, albeit in an unfortunately sensationalised and politicised way.[1,2]

As the quintessential human attribute, consciousness has long fascinated philosophers and scientists. The identification by Morruzi and Magoun[3] in the 1940s of the brain stem ascending reticular activating system (now simply called the reticular system) and its role in wakefulness clarified how higher brain centres are activated by diffuse afferents integrated in the brain stem that project to the thalamus and cortex. Although the ineffability and irreducibility of human conscious awareness discouraged attempts to precisely define it,[4] Plum and Posner[5] c larified that consciousness has two clinical dimensions: wakefulness and awareness. Cyclical wakefulness or alertness is provided by the reticular system and its projections to the thalamus. Awareness of self and the environment requires a functioning reticular system, but mainly relies on a functioning thalamus, cerebral cortex, and their white matter connections.[6] Disorders of consciousness result from interference with either or both of these systems.

Critical damage to the reticular system produces coma, a pathological state of eyes-closed unresponsiveness in which the patient lacks both wakefulness and awareness.[5] Critical damage to the thalami, cerebral cortex, or its connections, while sparing the reticular system, produces the vegetative state, in which the patient is awake but unaware. Pathological conditions that cause diffuse neuronal damage produce a continuous range of severity of neurological disorders from so-called brain death at its most extreme[7] to a fully reversible metabolic-toxic encephalopathy. To some extent, the boundaries that separate the defined clinical states are indistinct,[8] and each clinical state encompasses a range of severity—eg, deep coma without withdrawal or posturing versus light coma with withdrawal and posturing; vegetative state with electroencephalogram (EEG) electrocerebral silence[9] versus vegetative state with measurable EEG activity—within the continuum of global neuronal dysfunction.

Clinical disorders of consciousness can be acute and reversible, as in a transient stage in the spontaneous recovery after traumatic brain injury, or they can be irreversible and permanent, as in the cases of persistent vegetative state in which no recovery has occurred after many years. Here, I concentrate on the chronic, irreversible cases of vegetative state and minimally conscious state while recognising that many of the facts about clinical features, epidemiology, and pathophysiology apply to both the acute, reversible cases and the chronic, irreversible ones. My review format is a narrative not a systematic one given the nature of the published data (see search strategy).[10,11] My topic has been the subject of several other recent reviews.[12–15]

Background

Coma, a pathological state of eyes-closed unconsciousness from which patients cannot be aroused to wakefulness by stimuli, is caused by a structural, metabolic, or toxic disturbance of the reticular system and its thalamic projections.[5] In most survivors of comas who do not spontaneously achieve awareness, coma progresses after several weeks to a state of eyes-open wakefulness without

Search strategy and selection criteria

For this Seminar, I searched articles on PubMed in, or translated into, English published since 1990, using the terms "vegetative state" and "minimally conscious state". I also searched the reference lists from these articles, and analysed articles I have previously summarised.[10]

Panel 1: Criteria for diagnosis of persistent vegetative state[28,29]

All of the following features must be present except preserved cranial nerve reflexes

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

awareness, called the vegetative state.[5] True coma rarely persists for longer than a month in the absence of complicating metabolic, infectious, or toxic factors.

Bryan Jennett and Fred Plum[16] coined the term persistent vegetative state in a classic 1972 article in *The Lancet*. They chose the adjective vegetative because its definition in the Oxford English Dictionary captured the essential features of the patients: "a merely physical life, devoid of intellectual activity or social intercourse . . . an organic body capable of growth and development but devoid of sensation and thought." They defined persistent as presence for longer than a month. Persistent vegetative state does not necessarily imply permanence because it is a diagnostic, not a prognostic, term. Later, others proposed the term permanent vegetative state to refer to an irreversible vegetative state,[17] but with the two terms abbreviated in the same way—ie, PVS—confusion followed. It is clearer to drop the modifier entirely and to use vegetative state as a diagnosis; doctors should then issue a prognosis separately.[12,18,19]

Jennett and Plum pointed out that others had described similar cases before them, but earlier reports emphasised pathological over clinical features. Kretschmer[20] coined the name apallic state (later further delineated by Gerstenbrand and colleagues[21]) for a clinical and pathological disorder of diffuse cortical damage that, like vegetative state, features wakefulness with unresponsive unawareness. Cairns and colleagues[22] coined the term akinetic mutism to describe patients with damage to the bilateral orbitofrontal lobes who were awake but poorly responsive, and moved and spoke little. Later studies showed that lesions of the bilateral cingulate gyrus or their disconnections caused the syndrome.[23,24] Apallic state and akinetic mutism overlap with vegetative state and minimally conscious state. Because of the published rigorous definitions and criteria of vegetative state and minimally conscious state, these terms are generally preferred over those of apallic state and akinetic mutism.

Panel 2: Potential behavioural repertoire of patients in a persistent vegetative state[28,29]

- Sleep-wake cycles with eyes closed then open[32]
- Breathe spontaneously
- Blink and show roving eye movements
- Nystagmus
- Utter sounds but no words
- Brief, unsustained visual pursuit
- Grimace to pain, make facial expressions
- Yawn, make chewing jaw movements
- Swallow saliva
- Move limbs non-purposefully, arch back, decorticate limb posturing
- Flexion withdrawal from noxious stimuli[33]
- Move head or eyes briefly toward sound or movement
- Auditory startle
- Startle myoclonus
- Sleep-related erections[34]

Clinical features

Vegetative state

The essence of the vegetative state is wakefulness without awareness. Patients in vegetative state lie with their eyes open while awake and closed while asleep. They breathe spontaneously, have preserved autonomic function, and intact limb tendon and cranial nerve-innervated reflexes. They blink, have roving eye movements, and facial movements and expressions. They have limb spasticity, non-purposeful limb movements, and pseudobulbar palsy. But to the fullest extent determinable, they lack awareness of themselves and their environment. They cannot think, perceive, feel, or experience. Their wakefulness misleads others to assume they are sentient, yet the most careful bedside testing detects no reproducible and unequivocal evidence of awareness. Vegetative state in children older than age 1 year has the same essential clinical features as in adulthood,[25,26] but clinicians should carefully search for signs of conscious behaviour, which might be present in younger children presumed to be vegetative because of severe congenital brain damage.[27]

Two expert task forces empanelled in the 1990s authoritatively determined the medical facts of vegetative state. In the USA, the Multisociety Task Force on Persistent Vegetative State represented American neurological, neurosurgical, and paediatric neurology specialty societies, and published their report in 1994.[28] In the UK, the Royal College of Physicians Working Group published their report in 1996[29] with a clarification in 2003.[30] The American Neurological Association published an independent report on persistent vegetative state[31] in 1993, authored by their representative to the Multisociety Task Force, that was nearly identical to the report of the Task Force. Both groups undertook evidence-based reviews of published works, reviewed databases, and developed consensus-based guidelines for diagnosis and treatment that were largely congruent. The clinical features and potential behavioural repertoire of patients in vegetative state assembled by the task forces are listed in panel 1 and panel 2.[28,29,32–34] To diagnose vegetative state, all of the features in panel 1 must be present except preserved cranial nerve reflexes.

The Multisociety Task Force report was generally well received by the medical community,[35,36] but was criticised for not representing rehabilitation medicine,[37] for making glib assertions about the clinical assessment of awareness,[37] and for employing circular reasoning about awareness in their definition and conclusions.[38] The Multisociety Task Force acknowledged the biological limitations to knowing categorically that patients with vegetative state lack all awareness or capacity for suffering or experience because one person cannot directly experience the conscious life of another.[28] We can only interact with another person and make a reasoned judgment about their cognitive life on the basis of the quality of their responses to our stimuli. That we incorrectly deny the presence of their conscious life when it exists simply because we cannot measure it is, therefore, possible.[39] Despite this limitation, there are compelling reasons to conclude that patients in vegetative state utterly lack sentience based on neuroimaging, evoked potential, and neuropathological data.

Minimally conscious state

Some patients with global neuronal damage recover to a chronic state of poor responsiveness to stimuli, but show unequivocal—if intermittent and limited—evidence of awareness of themselves and their environment. The Aspen Neurobehavioral Conference expert panel formulated consensus-based diagnostic criteria for such patients whose clinical syndrome they termed the minimally conscious state.[40] They emphasised the qualitative difference between patients in minimally conscious state and vegetative state: although patients in both conditions are poorly responsive, those in a minimally conscious state retain measurable evidence of awareness whereas those in a vegetative state do not. They discussed the technical difficulty in assessing the precise cognitive and functional capacities of patients in minimally conscious state.[41] Their proposed diagnostic criteria and the potential behavioural repertoire of a patient are listed in panel 3 and panel 4. Minimally conscious state in children has the same essential features as in adults.[42,43]

Critics immediately questioned the usefulness and wisdom of creating a new diagnostic category for these disabled patients. First, although patients in a minimally conscious state had markedly impaired responsiveness but demonstrable awareness, it did not necessarily follow that their consciousness was minimal, as implied by the name of their diagnosis. A more accurate term for them is minimally responsive state,[44] as used in earlier reports of these patients.[45,46] Some critics expressed fear that the new diagnostic category could be misused politically to devalue the lives of disabled patients by allowing them to die more casually.[47] Others simply remained sceptical that there was a scientific justification for delineating a new and vaguely defined diagnostic category within the continuum of severely brain-injured patients.[48]

Panel 3: Criteria for diagnosis of minimally conscious state[39]

- Global impaired responsiveness
- Limited but discernible evidence of awareness of self and the environment as indicated by the presence of one or more of the following behaviours:
  - Following simple commands
  - Gestural or verbal responses to yes/no questions
  - Intelligible verbalisation
  - Purposeful behaviour: movements or affective behaviours that occur in contingent relation to relevant environmental stimuli and are not simply reflexive movements (see panel 4)

Assessment and differential diagnosis

The diagnosis of vegetative state and minimally conscious state can be made only after a careful assessment of the patient's level of awareness. The Glasgow coma scale, which was developed, validated, and used widely to assess the level of consciousness and prognosis of patients with acute traumatic brain injuries[49,50] and non-traumatic causes of coma,[51] is insufficient for the assessment of vegetative state and minimally conscious state because of its crude measurement of awareness and its omission of relevant neurological functions.[52] Clinicians who attempt to diagnose vegetative state or minimally conscious state can apply one of the sophisticated assessment methods that have been designed and validated to carefully identify subtle signs of awareness.[53] Systematic examinations are necessary to distinguish purely reflex responses to stimuli from responses that require awareness. Confidence in this important distinction is not always possible. Careful and repeated assessment is particularly important given the alarmingly high rate of error in diagnosing vegetative state reported in two series[54,55] of patients admitted to rehabilitation units, in which 37% and 43% of patients purportedly in vegetative state were identified on careful testing to have measurable awareness.

Sophisticated assessment methods have been developed and validated over the past decade for the measurement

Panel 4: Potential behavioural repertoire of patients in a minimally conscious state[39]

- Follow simple commands
- Gesture yes/no answers
- Make intelligible verbalisation
- Vocalisations or gestures in direct response to a question's linguistic content
- Reach for objects that demonstrates a clear association between object location and direction of reach
- Touch and hold objects in a way that accommodates the size and shape of the object
- Sustain visual pursuit to moving stimuli
- Smile or cry appropriately to linguistic or visual content of emotional but not to affectively neutral topics or stimuli

	Awareness	Wakefulness	Brain stem/ respiratory function	Motor reflexes	EEG	Evoked potentials	PET/fMRI	Comment
Brain death	Absent	Absent	Absent	Absent	Electrocerebral silence	Absent	Absent cortical metabolism	Legally dead in most jurisdictions
Coma	Absent	Absent	Depressed, variable	Reflex or posturing	Polymorphic delta, burst-suppression	BAER variable; cortical ERPs often absent	Resting <50%	Prognosis variable
Vegetative state	Absent	Present, intact sleep-wake cycles	Intact	Reflex, non-purposeful	Delta, theta, or electrocerebral silence	BAER preserved; cortical ERPs variable	Resting <50%; primary areas can be stimulated	Prognosis variable
Minimally conscious state	Intact but poorly responsive	Intact	Intact	Variable with purposeful movements	Non-specific slowing	BAER preserved; cortical ERPs often preserved	Reduced; secondary areas can be stimulated	Prognosis variable
Locked-in syndrome	Intact but communication difficult	Intact	Intact breathing; often brain stem signs	Quadriplegia, pseudobulbar palsy	Usually normal	BAER variable; cortical ERPs normal	Normal or nearly normal	Not a disorder of consciousness

*Electrocerebral silence; BAER=brain stem auditory evoked responses; ERP=event-related potentials. Table lists typical findings not necessarily present in all patients.

Table:* Comparison of vegetative state, minimally conscious state, and related disorders[28]

of awareness and neurobehavioural functioning in brain-injured patients.[56] There is wide variability in the psychometric integrity of the scales. The Western neurosensory stimulation profile, an early instrument,[57] does not target lower functioning patients, such as those in vegetative state and minimally conscious state.[58] The coma recovery scale integrates neuropsychological assessment into clinical assessment and has been validated in patients in vegetative state and minimally conscious state.[59] The Wessix head injury matrix requires no specific training[60] and facilitates data collection by multidisciplinary rehabilitation teams.[61]

Two comprehensive assessment scales developed within the past decade have been validated in patients in vegetative state and minimally conscious state, but need training to apply and are used almost exclusively in neurorehabilitation units. The sensory modality assessment and rehabilitation technique (SMART) was designed especially for patients in vegetative state,[62] correlates an appropriate rehabilitation programme for each level of function, and has been validated in patients in vegetative state and minimally conscious state.[63] The disorders of consciousness scale (DOCS) is a highly accurate tool for assessment of degree of awareness.[64] DOCS measures neurobehavioural integrity with a graded scale of responses to stimuli, rather than dichotomous all-or-none ratings in other scales, and provides systematic tracking and mapping of neurobehavioural recovery.[65]

Clinicians who assess awareness in unresponsive patients should administer various language, auditory, visual, somatosensory, and noxious stimuli, and judge whether the patient's responses are indicative of awareness or are merely reflex or random responses. Specifically, patients are given multiple simple commands to follow and visual stimuli to track with their eyes. The tests should be repeated to assess consistency if a response suggests awareness. Nursing personnel and family members can be asked whether they have witnessed any purposeful or aware behaviour, and asked to show it to the physician. Only in the utter absence of any response indicative of awareness should the diagnosis of vegetative state be considered.

Confounding variables should be reduced to a minimum to permit the examiner to elicit the patient's maximum performance.[13,40] The patient's arousal level can be enhanced by tapering sedating medications,[66] adequately stimulating the patient, and undertaking the examination in a distraction-free environment. Command-following tasks should elicit behaviours within the patient's physical capacity. Stimuli of all sensory modalities should be used. Assessments of responses should be done serially with validated quantitative methods. Observations of family-member and caregiver interactions with the patient should be included in the assessment. The examiner can consider standing the patient at 85° on a tilt table, because the upright position improves elicited neurobehavioural responses in some patients in vegetative state and minimally conscious state.[67]

The differential diagnosis of vegetative state and minimally conscious state (table) includes the locked-in syndrome, a condition of profound paralysis with intact consciousness and cognition that an unwary examiner might mistake for coma or vegetative state.[68] The classic locked-in syndrome, produced by a pontine haemorrhage or infarction, de-efferents all supranuclear motor pathways except those that control vertical eye movements, which are located rostral to the lesion.[69] Similar syndromes of utter paralysis with intact cognition can also be produced by endstage amyotrophic lateral sclerosis, advanced Guillain-Barré syndrome, myasthenia gravis, and other severe paralysing illnesses.[70]

The locked-in syndrome is not a disorder of consciousness, but can be mistaken for one. It is usually easy to distinguish on clinical grounds from vegetative state or minimally conscious state. In the classic pontine form of locked-in syndrome, pupils are pinpoint in size and the patient retains the capacity for voluntary vertical gaze and eye opening when asked.[69] In locked-in syndrome caused by severe peripheral paralysing disorders, these movements can be abolished, but clear evidence of peripheral nervous system paralysis and respiratory failure are present. Patients with locked-in syndrome usually have normal EEGs[71] and usually normal cerebral metabolism by PET scan,[72] consistent with their generally intact cognition.[73] Some patients with locked-in syndrome resulting from more diffuse brain injuries have mild but measurable cognitive dysfunction.[74]

Cause and epidemiology

The most common cause of vegetative state and minimally conscious state is traumatic brain injury.[75] Non-traumatic causes in adults include acute hypoxic-ischaemic neuronal injury suffered during cardiopulmonary arrest, stroke, and meningoencephalitis.[76] Although a few patients with endstage neurodegenerative diseases, such as Alzheimer's, Huntington's, and Parkinson's, might reach minimally conscious state if they survive long enough,[77] it is rare for them to progress to true vegetative state.[78] Causes of vegetative state in children include trauma, meningitis, asphyxia, congenital malformations, and perinatal injuries.[25,79] Children with anencephaly are arguably in a vegetative state, but children with less severe developmental disorders, such as hydranencephaly can show fragments of awareness behaviour when tested carefully.[27]

The prevalence of vegetative state has been estimated in several studies, but accurately measured in few. Based on several published prevalence surveys, the Multi-society Task Force claimed that there are 56–140 patients per million people with vegetative state in the USA.[28] This estimate was almost certainly high given that their prevalence model assumed that many patients with neurodegenerative diseases eventually progressed to a vegetative state (an assumption later discounted in an actual study[78]) and that many children were in a vegetative state from developmental malformations, another assumption shown to be overstated.[27] A carefully undertaken point prevalence study in Vienna in 2001,[80] based on individual case ascertainment, showed a vegetative state prevalence of 19 per million. This number is a more reliable prevalence measure than the estimates. The findings of a cross-sectional survey[81] done in 2000–03 of the prevalence of vegetative state in Dutch nursing homes indicated a prevalence of vegetative state lasting more than a month of two per million. The reason for this markedly lower prevalence is not clear, but might result from the home care of some patients in vegetative state or from treatment withdrawal decisions made earlier in the illness. The prevalence of minimally conscious state has not been carefully measured, but a Cochrane systematic review[82] of treatment programmes in minimally conscious state asserted that it was ten-fold greater than that of vegetative state.

Jennett[12] has reviewed and analysed the incidence data for vegetative state. The most reliable incidence data are for patients with traumatic brain injury. Moderate-to-severe traumatic brain injury has a yearly incidence of 250 per million population.[83] Of patients with severe traumatic brain injury with admission Glasgow coma scale scores of 8 or less, 6–16% remained vegetative at 1 month, of whom about 1% remained vegetative after 1 year.[84] Another 10–15% remained in a minimally conscious state.[83]

Pathology

Vegetative state and minimally conscious state are clinical syndromes that can be caused by several pathological processes. The pathology of vegetative state is more completely described than that of minimally conscious state. The latter usually represents less severe pathological changes than the former with less thalamic injury and less high-grade diffuse axonal injury.[85]

The pathology of vegetative state can be described anatomically and histologically. Anatomically, vegetative state is caused by lesions that diffusely damage cortical neurons, the thalami, or the white matter tracts that connect the thalami and cortex, but that spare the brain stem and hypothalamus.[86] Histologically, the processes can be divided into traumatic brain injury and non-traumatic types. As a general rule, traumatic brain injury damages the white matter tracts more than the grey matter; non-traumatic disorders show the opposite distribution.[86]

Traumatic brain injury produces characteristic diffuse white matter lesions called diffuse axonal injury. This type of injury is produced from a severe rotational traumatic brain injury in which the different torques induced in dense grey matter and less dense white matter exert a shearing effect on the axons and diffusely sever them.[87] There are associated small haemorrhages in the white matter as a result of diffuse axonal injury that can be seen on MRI.[88] The severed axons disconnect the thalami from the cortex and isolate cortical areas from each other. Most patients with severe traumatic brain injury have comorbid brain injuries that additionally damage neurons, including cortical contusions, intracerebral haemorrhages, and raised intracranial pressure.[89,90]

Non-traumatic cases of vegetative state that result from diffuse hypoxic-ischaemic insults produce widespread damage to cortical and thalamic neurons out of proportion to brain stem neurons because higher metabolic demands render them more susceptible.[91] A pattern of layered cortical neuronal damage called laminar necrosis is common in the cardiopulmonary arrest cases. Diffuse boundary-zone infarcts are seen in patients who develop vegetative state from severe hypotension.[86] The importance of profound thalamic damage was emphasised in the pathological findings of a famous patient with hypoxic-ischaemic vegetative state—Karen Ann Quinlan.[92] The findings of a study[93] of the thalamus in minimally conscious state and vegetative state show the dorsomedial and ventral posterior thalamic nuclei to be preferentially damaged. The brain of another highly publicised patient with hypoxic-ischaemic vegetative state—Theresa Schiavo—showed striking and global cortical laminar necrosis worst in arterial border zones, total loss of basal ganglia and thalamic neurons, and weighed only 615 g.[94]

Neuroimaging

Anatomical brain imaging discloses few features of diagnostic specificity for vegetative state and minimally conscious state, but functional brain imaging reveals findings of importance in understanding how consciousness is mapped in the brain that will become diagnostically useful in the near future. Brain imaging with CT and MRI in vegetative state shows widespread cortical and thalamic atrophy that increases in severity after months to years.[12] Anatomical MRI sequences at 6 weeks after traumatic brain injury, alone, are a poor discriminator of patients in vegetative state who will regain awareness from those who will not.[95,96] Diffusion-weighted MRI sequences obtained within a week after a hypoxic-ischaemic injury are a better predictor of later improvement. The presence of large, symmetrical areas of restricted diffusion, particularly in the hemispheric white matter, is an early poor prognostic sign.[97,98]

Studies of functional brain imaging with fMRI and PET have disclosed exciting findings that, once validated by additional studies in larger groups of patients, could help discriminate vegetative state from coma, minimally conscious state, and other states of impaired consciousness.[14] PET studies of patients in coma from traumatic brain injury or non-traumatic causes show a reduction of grey matter metabolic rates in the 50–70% range[99,100] that are similar to levels of normal patients undergoing general anaesthesia.[101,102] But PET studies in coma are not useful clinically because they correlate neither with Glasgow coma scale scores[103,104] nor outcomes.[105]

Several studies of resting brain function in vegetative state by PET (reviewed by Laureys and colleagues[14]) show a baseline decrease in cortical metabolism to 40–50% of normal values.[106–110] This reduction worsens over time in vegetative state as a result of Wallerian and trans-synaptic neuronal degeneration, but generally spares the brain stem and hypothalamus.[110] Certain cortical areas in the prefrontal, posterior parietal, and parieto-temporal regions, and Broca's area that are necessary for attention, language, and memory are particularly affected[111] as is their connectivity.[112] When patients in vegetative state later recover awareness, there is a concomitant improvement in both cortical metabolism[108] and connectivity[113] in affected areas. These data suggest that the observed baseline reduction in resting cerebral metabolism represents a combination of potentially reversible neuronal metabolic dysfunction and irreversible neuronal death.[114]

Of greater relevance are studies of cortical activation in patients in vegetative state with auditory, visual, and somatosensory stimuli. In general, these stimuli activate primary cortical areas but do not activate secondary cortical areas (believed to be necessary for awareness), which are functionally disconnected from the primary cortical regions.[14,115] Results of studies in patients in vegetative state show that auditory stimuli activate the superior temporal gyrus,[110,116] visual stimuli activate the calcarine cortex,[117] and noxious somasthetic stimuli activate the midbrain, thalamus, and somatosensory cortex.[118] The absence of activation of higher order multimodal association cortices that provide the brain's integrated, distributed neuronal networks is evidence that patients in vegetative state lack awareness.[14]

PET and fMRI studies of patients in minimally conscious state show markedly greater distributed neural network activation than in those in vegetative state. Baseline cortical metabolic rates of patients in minimally conscious state are reduced to levels only slightly above those in vegetative state but show greater activation of the medial parietal and posterior cingulate cortices,[119] those metabolically active regions believed to be necessary for human awareness.[120,121] The findings of PET and fMRI studies, using voice auditory stimuli in several patients in minimally conscious state, show striking and widespread activation of distributed cortical neuronal networks that are normal or close to normal values.[122–124] These preliminary functional imaging data suggest that some patients in minimally conscious state retain sufficient cortical connectivity to support cognitive and linguistic processes,[125] and might not be as minimally conscious as their impaired responsiveness suggests.[44]

A few brain-injured patients occupy a middle ground between vegetative state and minimally conscious state, showing typical findings of vegetative state but also demonstrating isolated behavioural fragments atypical for vegetative state.[107] In one carefully reported case,[126] a patient with otherwise typical vegetative state for 20 years uttered single meaningless words unrelated to context. PET showed widespread suppression of cerebral metabolism typical of vegetative state, but with partial preservation of the perisylvian language network.[126]

Electrophysiology

Electroencephalography discloses non-specific findings in vegetative state and minimally conscious state. Most patients in vegetative state have profound generalised slowing of background activity with delta rhythms that do not react to stimuli,[127,128] but that desynchronise with sleep.[28] Patients with the most severe forms of vegetative state show electrocerebral silence.[9] Recovery of awareness is associated with re-establishment of the alpha rhythm.[127] There are few systematic data on EEG in minimally conscious state, but most patients show diffuse slowing in the theta or delta range.[13]

Studies of event-related potential (ERP) have limited diagnostic and prognostic use in vegetative state. Brain stem auditory evoked responses are usually preserved, indicating sparing of brain stem neurons. Cortical ERPs by somatosensory or auditory stimulation can be present or absent in vegetative state.[129–131] If they are absent bilaterally a week after the injury, the prognosis for return of awareness is poor.[132–135] The findings of one study[110] indicated their presence in primary cortical areas but their absence in secondary and association cortical areas, paralleling PET stimulation neuronal metabolism data. Findings of another study[136] showed cortical ERPs to be present in all patients in vegetative state whose background EEG activity was greater than 4 Hz but absent in most of those whose EEG activity was less than 4 Hz. And findings of a study by Luaaute and colleagues[137] showed a strong correlation between the return of ERPs and good neurological outcome. The presence of cortical ERPs does not, however, necessarily imply awareness.[138] Results of a study,[139] correlating quantitative EEG and PET regional metabolic rates, showed that the normal homoeostatic coupling of neuronal electrical functioning to neuronal metabolic activity was absent in vegetative state but remained present in minimally conscious state.

Prognosis

Patients might be in a vegetative state or minimally conscious state temporarily as a stage during recovery from a traumatic brain injury or a non-traumatic brain insult, or might reside in the state chronically and permanently. The issue of prognosis for recovery of awareness is a crucial but difficult clinical determination. The Multisociety Task Force devoted nearly half of its effort to reviewing published data on recovery and proposing guidelines for estimation of prognosis.[28] They formulated several principles. First, the prognosis for regaining awareness from non-traumatic (especially hypoxic-ischaemic) coma or vegetative state is worse than for an equivalent state that results from traumatic brain injury. Second, the longer patients remain in a vegetative state, the less likely they are to eventually regain awareness. Finally, prognoses for recovering awareness can be expressed only as probabilities with confidence intervals. The Task Force concluded that the probability of recovery of awareness is very small (<1%) after 3 months in a non-traumatic vegetative state or after 12 months in a traumatic vegetative state.[28] They asserted that the vegetative state could be considered permanent at those points, although they acknowledged the statistical limitations of these conclusions because of the small number of patients in vegetative state alive at 12 months and the existence of several well documented cases of late recoveries of awareness that fell outside of those parameters.[140–144]

The second prognostic issue the Task Force addressed was life expectancy. This, too, is a difficult estimate because of the non-uniform treatment given to the patients comprising the studies. Nevertheless, they stated the mortality of the vegetative state to be 70% at 3 years and 84% at 5 years.[145] The limitation of applying these data prospectively has been called the fallacy of the self-fulfilling prophecy.[146,147] The life expectancy data in these studies are experiential and uncontrolled because not all patients were given the most aggressive life-sustaining treatment. Many, perhaps most, patients who died were permitted to die from infection or other potentially treatable causes. Although the decision-making about treatment in individual cases might have been ethically sound, these data are a misleading indicator of life expectancy with treatment. Indeed, some young patients in vegetative state without serious co-morbidities can survive for decades with only artificial nutrition and hydration.

Several investigators have attempted to enhance prognostication in vegetative state with ancillary testing. The bilateral absence of the cortical ERP N20 was associated with 100% mortality in patients in non-traumatic coma or vegetative state.[148] The findings of a meta-analysis of early predictors of poor outcome after hypoxic-ischaemic coma or vegetative state showed that the bilateral absence of cortical ERPs were most highly predictive of non-awakening.[149] The presence of MRI-documented haemorrhages of the corpus callosum or brain stem were predictive of non-recovery from vegetative state after diffuse axonal injury induced by traumatic brain injury.[95]

There are fewer reliable data on prognostic indicators in minimally conscious state. Similar to vegetative state, the longer minimally conscious state persists, the lower the probability of recovery. In the subgroup of patients initially in minimally conscious state from acute traumatic brain injury, 40% will regain full consciousness within 12 weeks of injury, and up to 50% will regain independent function at 1 year.[150] But in the subgroup of severely injured patients in prolonged minimally conscious state, findings of one study[151] showed a heterogeneity of outcome without reliable early predictors.

Medical treatment

After discharge from the intensive care unit, patients in vegetative state require the same level of medical and nursing care as comatose patients, including, positioning, range of motion exercises, pulmonary toilet, skin care, bowel and bladder care, and optimum nutrition.[152] All patients require gastrostomy for tube feedings and nearly all have a tracheostomy for airway protection, but no longer require mechanical ventilation. Treatment in a neurorehabilitation unit that specialises in brain injury is ideal[153] because of preliminary evidence that early intensive neurorehabilitation improves outcome.[154] Spasticity is often severe and requires aggressive treatment.[155] Patients in minimally conscious state might need individualised communication systems developed by speech and language therapists.

Attempts to improve the responsiveness of the patient in vegetative state with sensory, electrical, and pharmacological stimulation have been disappointing, but most studies represent class III evidence, making firm conclusions hard to draw. Sensory stimulation programmes that provide music, voices, visual images, smells, and touching are widespread and have strong intuitive appeal. But systematic reviews[82,156] of these therapies have not shown convincing efficacy in improving awareness. Similarly, deep-brain electrical stimulation of the thalamus or mesencephalic reticular formation, although having a theoretical basis, have shown no unequivocal benefit.[157,158] Pharmacological treatment has been attempted with various drugs, including levodopa,[159–161] amphetamines,[162] tricyclic antidepressants,[163] amantadine,[164] bromocriptine,[165] anticonvulsants,[166] and others.[167] Levodopa and amantadine might be useful when parkinsonian features are present,[168,169] but they are more likely to benefit patients in minimally conscious state than those in vegetative state.[170–172] Clinicians should carefully consider the benefits and risks of initiating trials of stimulant medications to enhance function in patients in minimally conscious state.[172]

Ethical and legal issues

Management of patients in vegetative state or minimally conscious state inevitably raises ethical and legal questions about the appropriate degree of life-sustaining treatment. Most ethical analyses conclude that the decision to treat aggressively or passively should be guided by reliable information about how the patient would wish to be treated in this condition,[10,12,173] in accordance with the principles of patient-centred medicine.[174] Physicians can seek this information in advance directives and by speaking with the patient's family, friends, and primary-care physician.[175] Once it is reliably established how the patient wished to be treated, it is within the standards of accepted medical practice to treat patients in vegetative state and minimally conscious state aggressively to permit them to live as long as possible, or to withhold life-sustaining therapy, including artificial hydration and nutrition, to allow them to die.[173,176] Disputes among family members over the nature of the patient's true wishes can be mediated by a hospital ethics committee and, if unresolved, referred to court for judicial review. The patient's prognosis for functional recovery is an essential element in identifying the appropriate level of treatment, and should be stated clearly.[177,178]

Guidelines for management of patients in vegetative state that incorporate these principles have been published by the American Medical Association,[179] the American Academy of Neurology,[180,181] the American Neurological Association,[31] the British Medical Association,[182] the Royal College of Physicians,[29,30] the Italian Neurological Society,[183] and the World Medical Association.[184] Surveys of American[185] and British[186] neurologists and neurosurgeons generally show support for these positions, though they also reveal the expected diversity of opinion on questions of diagnosis and treatment. Japanese physicians are more likely to insist on aggressive medical treatment than their British or American colleagues.[187] A survey[188] of American neurologists revealed an unfortunate degree of ignorance about established ethical and legal decision-making standards.

Precedent-setting judicial rulings have established legal standards of decision-making for patients in vegetative state and minimally conscious state.[189] The US Supreme Court ruled in *Cruzan* that all citizens have a constitutionally protected right to refuse life-sustaining therapy, including artificial hydration and nutrition, and that this right can be exercised by a surrogate decision-maker on the patient's behalf.[190] In the UK, the Family Division of the High Court in London ruled in *Bland* that artificial hydration and nutrition could be removed from a patient in persistent vegetative state.[191] The California Supreme Court in *Wendland* ruled that the feeding tube of a patient in minimally conscious state could not be removed as requested by family members because he was not terminally ill.[192] Jennett[12] has reviewed the relevant laws and judicial rulings on patients in vegetative state and minimally conscious state in developed countries.

Future directions

Several areas are ready for further research. The intensive study of additional patients in vegetative state and minimally conscious state by PET, fMRI, cortical ERPs, and magnetoencephalography will probably yield information of sufficient specificity about how consciousness is mapped in the brain to quantify the extent of awareness, help confidently discriminate between vegetative state and minimally conscious state, and improve predictions with respect to recovery.[125] Further trials of stimulant medications could clarify which patients in minimally conscious state are most likely to respond. Ethical issues that need to be resolved include identifying when a patient in vegetative state or minimally conscious state can be used as a research participant,[193] the management of pregnancy in these patients,[194] the degree of certainty about prognosis and patient preference for treatment that is sufficient to discontinue artificial hydration or nutrition,[195,196] the role of cost-effectiveness analysis in bedside decisions about treatment,[197] and the neuroethics philosophical questions raised by functional neuroimaging data about normality and personal identity.[198]

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