MEDICAL ASPECTS OF THE PERSISTENT VEGETATIVE STATE

(First of Two Parts)

THE MULTI-SOCIETY TASK FORCE ON PVS*

Abstract This consensus statement of the Multi-Society Task Force summarizes current knowledge of the medical aspects of the persistent vegetative state in adults and children.

The vegetative state is a clinical condition of complete unawareness of the self and the environment, accompanied by sleep–wake cycles, with either complete or partial preservation of hypothalamic and brain-stem autonomic functions. In addition, patients in a vegetative state show no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; show no evidence of language comprehension or expression; have bowel and bladder incontinence; and have variably preserved cranial-nerve and spinal reflexes. We define persistent vegetative state as a vegetative state present one month after acute traumatic or nontraumatic brain injury or lasting for at least one month in patients with degenerative or metabolic disorders or developmental malformations.

The clinical course and outcome of a persistent vegetative state depend on its cause. Three categories of disorder can cause such a state: acute traumatic and nontraumatic brain injuries, degenerative and metabolic brain disorders, and severe congenital malformations of the nervous system.

Recovery of consciousness from a posttraumatic persistent vegetative state is unlikely after 12 months in adults and children. Recovery from a nontraumatic persistent vegetative state after three months is exceedingly rare in both adults and children. Patients with degenerative or metabolic disorders or congenital malformations who remain in a persistent vegetative state for several months are unlikely to recover consciousness. The life span of adults and children in such a state is substantially reduced. For most such patients, life expectancy ranges from 2 to 5 years; survival beyond 10 years is unusual. (N Engl J Med 1994;330:1499-508.)

THE term "persistent vegetative state" was coined by Jennett and Plum in 1972 to describe the condition of patients with severe brain damage in whom coma has progressed to a state of wakefulness without detectable awareness.[1] Such patients have sleep–wake cycles but no ascertainable cerebral cortical function. Jennett and Plum thought that patients in a persistent vegetative state could be distinguished clinically from those with other conditions associated with prolonged unconsciousness.

In 1983 the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research accepted the definition of persistent vegetative state proposed by Jennett and Plum and defined unconsciousness as the inability "to experience the environment." In the commission's judgment, a persistent vegetative state is only one form of permanent unconsciousness.[2] The others include coma after a traumatic or nontraumatic injury, with death occurring before the recovery of sufficient brain-stem function to allow a stable vegetative state; the end stages of degenerative neurologic conditions, such as Alzheimer's or Creutzfeldt–Jakob disease; coma from untreatable mass lesions such as neoplasms or vascular masses; and anencephaly in infants.

Because of the diagnostic, prognostic, and therapeutic uncertainties concerning the persistent vegetative state, several professional medical organizations began a comprehensive examination of their standards of medical care for patients with this condition.[3-7] In 1989, the American Academy of Neurology published a position paper that defined persistent vegetative state, classified artificial nutrition and hydration as forms of medical treatment, and stated that patients or their surrogates could decide to terminate treatment and that there were no medical or ethical distinctions between withholding and withdrawing treatment.[8] A 1990 survey by the American Neurological Association found that 88 percent of responding members agreed with this document.[9] In a 1991 survey by the Child Neurology Society, 92 percent of respondents agreed with the position paper as it related to adults, but only 72 percent thought that it was applicable to infants and children.[10] In addition, 75 percent of the respondents to this survey indicated that they would not withdraw nutrition and hydration from children in a persistent vegetative state.

In 1990, the Council on Scientific Affairs and the Council on Ethical and Judicial Affairs of the American Medical Association issued a report that provided

Address reprint requests to the Multi-Society Task Force on PVS, American Academy of Neurology, 2221 University Ave. S.E., Minneapolis, MN 55414.

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*The members of the task force are Stephen Ashwal, M.D., cochairman (Loma Linda University School of Medicine, Loma Linda, Calif.), Child Neurology Society; Ronald Cranford, M.D., cochairman (Hennepin County Medical Center, Minneapolis), American Academy of Neurology; James L. Bernat, M.D. (Dartmouth Medical School, Hanover, N.H.), American Academy of Neurology; Gastone Celesia, M.D. (Loyola University Stritch School of Medicine, Maywood, Ill.), American Neurological Association; David Coulter, M.D. (Boston University School of Medicine, Boston), Child Neurology Society; Howard Eisenberg, M.D. (Maryland Institute of Emergency Medical Services Systems, Baltimore), American Association of Neurological Surgeons; Edwin Myer, M.D. (Medical College of Virginia, Richmond), American Academy of Pediatrics; Fred Plum, M.D. (New York Hospital–Cornell University Medical College, New York), American Neurological Association; Marion Walker, M.D. (Primary Children's Hospital and Medical Center, Salt Lake City), American Academy of Pediatrics; Clark Watts, M.D. (University of Texas Health Sciences Center, San Antonio), American Association of Neurological Surgeons; and Teresa Rogstad, project administrator, American Academy of Neurology.

clinical criteria for the diagnosis of a persistent vegetative state and discussed ethical and legal implications of decisions to withhold or withdraw life-prolonging medical treatment — matters that were receiving widespread attention at the time.[11-15] In 1991, the United Kingdom's Institute of Medical Ethics Working Party on the Ethics of Prolonging Life and Assisting Death published a position statement indicating that a diagnosis of persistent vegetative state could usually be made with confidence three months after the acute insult but that in young children, the extent of damage and period of recovery were less predictable.[16] More recently, the British Medical Association's Medical Ethics Committee and the American Neurological Association have published position papers that define criteria for the clinical diagnosis of a persistent vegetative state and address several of the ethical issues concerning the care of patients in such a state.[17,18]

Because of the acceptance of recent consensus statements concerning guidelines for determining brain death in children[19] and the medical aspects of anencephaly in infants,[20] the Multi-Society Task Force on PVS was established in 1991 and charged with the creation of this document. Two representatives were appointed from each of the five societies, and an advisory panel of consultants was selected from the related fields of medicine, ethics, and law. The document was approved by the executive committee of each society.

Data reviewed by members of the task force were obtained from several sources, including a comprehensive literature review of all Medline references to the terms "vegetative state" and "persistent vegetative state," a "request for information" published in medical journals supported by the five sponsoring societies, a review of stories in the popular media concerning unexpected recovery from prolonged coma, and data from the National Institute of Neurological Disorders and Stroke Traumatic Coma Data Bank.

This statement by the task force summarizes the medical facts about the persistent vegetative state; it does not address associated ethical, legal, or other issues. The statement is divided into two parts. The first defines persistent vegetative state and related terms and conditions and discusses the epidemiology, causes, and pathological features, as well as ancillary diagnostic studies. The second part addresses the prognosis for recovery and long-term survival of patients in a persistent vegetative state and discusses issues related to pain and suffering and treatment.

Definition and Clinical Aspects

The vegetative state is a clinical condition of complete unawareness of the self and the environment, accompanied by sleep–wake cycles with either complete or partial preservation of hypothalamic and brain-stem autonomic functions. The condition may be transient, marking a stage in the recovery from severe acute or chronic brain damage, or permanent, as a consequence of the failure to recover from such injuries. The vegetative state can also occur as a result of the relentless progression of degenerative or metabolic neurologic diseases or from developmental malformations of the nervous system.

The vegetative state can be diagnosed according to the following criteria: (1) no evidence of awareness of self or environment and an inability to interact with others; (2) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness manifested by the presence of sleep–wake cycles; (5) sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical and nursing care; (6) bowel and bladder incontinence; and (7) variably preserved cranial-nerve reflexes (pupillary, oculocephalic, corneal, vestibulo-ocular, and gag) and spinal reflexes.

The distinguishing feature of the vegetative state is an irregular but cyclic state of circadian sleeping and waking unaccompanied by any behaviorally detectable expression of self-awareness, specific recognition of external stimuli, or consistent evidence of attention or intention or learned responses. Patients in a vegetative state are usually not immobile. They may move the trunk or limbs in meaningless ways. They may occasionally smile, and a few may even shed tears; some utter grunts or, on rare occasions, moan or scream. Some patients have acquired, nonhabitual startle myoclonus. Such activities are inconsistent, nonpurposeful, and coordinated only when they are expressed as part of a subcortical, instinctively patterned, reflexive response to external stimulation. These motor activities may misleadingly suggest purposeful movements, yet these responses have been observed in patients in whom careful study has disclosed no evidence of psychological awareness or the capacity to engage in learned behavior.

As a result of the relative preservation of brain-stem functions, most patients in a vegetative state retain good to normal reflexive regulation of vision and eye movement. Some patients have unequal or irregular pupils or limited responses to vestibulo-ocular stimulation. A few patients may have signs of mild internuclear ophthalmoplegia or other oculomotor abnormalities related to the brain stem. Occasionally, one or both third nerves are paralyzed.

Sustained visual pursuit is lacking in most patients in a vegetative state. They do not fixate on a visual target, track moving objects with their eyes, or withdraw from threatening gestures. When patients undergo a transition from the vegetative state to a state of awareness, one of the first and most readily observable signs of this transition is the appearance of sustained visual pursuit. However, patients in a vegetative state often have inconsistent primitive auditory or visual orienting reflexes, characterized by a turning of the head and eyes toward peripheral sounds or movements. In rare cases, patients who have no other evidence of consciousness over a period of months to years have some degree of briefly sustained visual pursuit or fixation, which is believed to be mediated through brain-stem structures. Nevertheless, one should be extremely cautious in making a diagnosis of the vegetative state when there is any degree of sustained visual pursuit, consistent and reproducible visual fixation, or response to threatening gestures.

The capacity for survival in a persistent vegetative state requires preservation of hypothalamic and brain-stem autonomic functions. Most patients who survive for a long time maintain normal body temperature, the ability to breathe spontaneously, and a functioning cardiovascular system. The prognosis is worse if there are hypothalamic disturbances producing central fever, excess sweating, disturbances in salt and water metabolism, and refractory pulmonary problems. In most patients, the gag, cough, sucking, and swallowing reflexes are preserved. Except for a lack of coordination in chewing and swallowing, gastrointestinal function remains nearly normal. As the prolonged survival of some patients in a persistent vegetative state suggests, autonomic function is sufficient to maintain long-term internal regulation so long as external needs receive constant attention.

Related Terms and Conditions

Unconsciousness, Coma, and the Vegetative State

The term "consciousness" was defined by William James in 1890 as awareness of the self and the environment. Consciousness has two dimensions: wakefulness and awareness. Normal consciousness requires arousal, an independent, autonomic–vegetative brain function subserved by ascending stimuli from the pontine tegmentum, posterior hypothalamus, and thalamus that activate wakefulness. Awareness is subserved by cerebral cortical neurons and their reciprocal projections to and from the major subcortical nuclei. Awareness requires wakefulness, but wakefulness can be present without awareness.

Unconsciousness implies global or total unawareness and is characteristic of both coma and the vegetative state. Patients in a coma are unconscious because they lack both wakefulness and awareness. Patients in a vegetative state are unconscious because, although they are wakeful, they lack awareness. In this report we use the terms awareness and consciousness interchangeably.

Persistent as Compared with Permanent Vegetative States

As originally defined by Jennett and Plum in 1972, the term "persistent," when applied to the vegetative state, meant sustained over time; "permanent" meant irreversible.[1] Notwithstanding Jennett and Plum's precise use of language, confusion has arisen over the exact meaning of the term "persistent." The adjective "persistent" refers only to a condition of past and continuing disability with an uncertain future, whereas "permanent" implies irreversibility. Persistent vegetative state is a diagnosis; permanent vegetative state is a prognosis.

A wakeful unconscious state that lasts longer than a few weeks is referred to as a persistent vegetative state. We define such a state operationally as a vegetative state present one month after an acute traumatic or nontraumatic brain injury or a vegetative state of at least one month's duration in patients with degenerative or metabolic disorders or developmental malformations. A permanent vegetative state, on the other hand, means an irreversible state, which like all clinical diagnoses in medicine, is based on probabilities, not absolutes. A patient in a persistent vegetative state becomes permanently vegetative when the diagnosis of irreversibility can be established with a high degree of clinical certainty — that is, when the chance that the patient will regain consciousness is exceedingly small. We believe there are sufficient data on the prognosis for neurologic recovery to allow us to distinguish between persistent and permanent vegetative states. These data, in conjunction with other relevant factors in an individual patient, can be used by a physician to determine when the persistent vegetative state becomes permanent — that is, when a physician can tell the patient's family or surrogate with a high degree of medical certainty that there is no further hope for recovery of consciousness or that, if consciousness were recovered, the patient would be left severely disabled.

Diagnostic Factors and the Limits of Certainty

By definition, patients in a persistent vegetative state are unaware of themselves or their environment. They are noncognitive, nonsentient, and incapable of conscious experience. There is, however, a biologic limitation to the certainty of this definition, since we can only infer the presence or absence of conscious experience in another person.[21] A false positive diagnosis of a persistent vegetative state could occur if it was concluded that a person lacked awareness when, in fact, he or she was aware. Such an error might occur if a patient in a locked-in state (i.e., conscious yet unable to communicate because of severe paralysis) was wrongly judged to be unaware. Thus, it is theoretically possible that a patient who appears to be in a persistent vegetative state retains awareness but shows no evidence of it. In the practice of neurology, this possibility is sufficiently rare that it does not interfere with a clinical diagnosis carefully established by experts.

Several individual signs of unconsciousness, as well as a small number of laboratory tests, are very closely correlated with the diagnosis of the condition of unconsciousness that characterizes a persistent vegetative state. At present, three lines of evidence based on careful clinical and laboratory studies support the conclusion that patients in a persistent vegetative state are unaware of themselves or their environment.[8,11,21] First, motor or eye movements and facial expressions in response to various stimuli occur in stereotyped patterns that indicate reflexive responses integrated at deep subcortical levels rather than learned voluntary acts. The presence of these responses is consistent with complete unawareness. Second, positron-emission tomographic studies of regional cerebral glucose metabolism show levels far lower than those in patients who are aware or in a locked-in state. These low metabolic rates are comparable to those reported during deep general anesthesia in normal subjects whom all would agree are unaware and insensate.[22] Finally, all available neuropathological examinations of the brains of patients with a clinical diagnosis of a persistent vegetative state show lesions so severe and diffuse that awareness would have been highly improbable, given our biologic understanding of how the anatomy and physiology of the brain contribute to consciousness.[23,24]

An accurate diagnosis is critical. Errors in diagnosis have occurred because of confusion about the terminology used to describe patients in this condition, the inexperience of the examiner, or an insufficient period of observation.[25] Physicians caring for such patients should be aware of these potential problems and be as precise and careful as possible when applying the suggested clinical criteria.[26]

Related Conditions

Other conditions of severe neurologic disability or altered consciousness include coma, brain death, the locked-in syndrome, and dementia (Table 1).

Coma is deep, sustained pathologic unconsciousness that results from dysfunction of the ascending reticular activating system in either the brain stem or both cerebral hemispheres. The eyes remain closed, and the patient cannot be aroused. To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness, coma must persist for at least an hour.

Brain death is the permanent absence of all brain functions, including those of the brain stem. Brain-dead patients are irreversibly comatose and apneic and have lost all brain-stem reflexes and cranial-nerve functions. The standard clinical criteria for the diagnosis of brain death in adults, children, and newborn infants are outlined elsewhere.[14,19,27-30]

The locked-in syndrome refers to a state in which consciousness and cognition are retained but movement and communication are impossible because of severe paralysis of the voluntary motor system.[28,31] This condition may result from abnormalities in the descending corticospinal and corticobulbar pathways at or below the pons. In such cases, breathing is possible. The locked-in syndrome can also be associated with diseases of the peripheral motor nerves or paralysis produced by the administration of neuromuscular blocking agents. Patients with this syndrome can usually establish limited communication through eye-movement signals. Diagnosis of the locked-in syndrome is established by clinical examination. Brain imaging may show isolated ventral pontine infarction, and nerve-conduction studies may demonstrate severe peripheral neuropathy. Positron-emission tomographic scans have shown higher metabolic levels in the brains of patients in the locked-in state than in patients in a persistent vegetative state. Electroencephalograms, evoked responses, and single-photon-emission computed tomograms do not distinguish reliably between the locked-in and vegetative states.

Dementia is a condition of progressive, multidimen-

Table 1. Characteristics of the Persistent Vegetative State and Related Conditions.*

Condition	Self-Awareness	Sleep–Wake Cycles	Motor Function	Experience of Suffering	Respiratory Function	EEG Activity	Cerebral Metabolism†	Prognosis for Neurologic Recovery
Persistent vegetative state	Absent	Intact	No purposeful movement	No	Normal	Polymorphic delta or theta, sometimes slow alpha	Reduced by 50% or more	Depends on cause (acute traumatic or nontraumatic injury, degenerative or metabolic condition, or developmental malformation)
Coma	Absent	Absent	No purposeful movement	No	Depressed, variable	Polymorphic delta or theta	Reduced by 50% or more (depends on cause)	Usually recovery, persistent vegetative state, or death in 2 to 4 weeks
Brain death	Absent	Absent	None or only reflex spinal movements	No	Absent	Electrocerebral silence	Absent	No recovery
Locked-in syndrome	Present	Intact	Quadriplegia and pseudobulbar palsy; eye movement preserved	Yes	Normal	Normal or minimally abnormal	Minimally or moderately reduced	Recovery unlikely; persistent quadriplegia with prolonged survival possible
Akinetic mutism	Present	Intact	Paucity of movement	Yes	Normal	Nonspecific slowing	Unknown	Recovery very unlikely (depends on cause)
Dementia	Present but lost in late stages	Intact	Variable; limited with progression	Yes but lost in late stages	Normal	Nonspecific slowing	Variably reduced	Irreversible (ultimate outcome depends on cause)

*This table provides a general overview of the persistent vegetative state and related neurologic conditions. Because of the overlap between clinical and laboratory findings, these characteristics will not apply to every patient. Neuroimaging studies (magnetic resonance imaging or computed tomography) may be useful in the clinical evaluation of patients but may not always be helpful in differentiating among these conditions. EEG denotes electroencephalographic.

†Determined by positron-emission or single-photon-emission computed tomography.

sional loss of cognitive functions in which arousal mechanisms are usually normal. Advanced dementia can progress until patients lose their self-awareness and all evidence of learned behavior. At this point, such patients are in a vegetative state.

Three other conditions deserve mention. Akinetic mutism is a rare syndrome characterized by pathologically slowed or nearly absent bodily movement and loss of speech.[28] Wakefulness and self-awareness may be preserved, but the level of mental function is reduced. The condition characteristically accompanies gradually developing or subacute bilateral damage to the paramedian mesencephalon, basal diencephalon, or inferior frontal lobes. Neocortical death is a term used by some authors to refer to a persistent vegetative state, but in addition to the characteristics of a persistent vegetative state, neocortical death is marked by an absence or substantial slowing of electrocortical activity on electroencephalography. Others equate neocortical death with the ostensible death of all neurons of the cerebral cortex. It is not clear, therefore, whether this term denotes a clinical syndrome or its electrical, pathologic, or anatomical features. Apallic syndrome is an archaic term for a condition that is now considered equivalent to a persistent vegetative state.[32] The terms "neocortical death" and "apallic state" have limited usefulness and should be abandoned, because they do not represent distinct clinical entities.

Epidemiology

The prevalence of persistent vegetative state is not known because of the lack of accepted diagnostic criteria and the fact that, until recently, neither the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM), nor most health agencies included persistent vegetative state as a codable diagnosis. According to estimates, however, in the United States there are 10,000 to 25,000 adults and 4,000 to 10,000 children in a persistent vegetative state.[6,10,11,15,16,33-47]

Table 2. Causes of the Persistent Vegetative State in Adults and Children.*

Acute injuries
Traumatic
Motor vehicle accidents
Gunshot wound or other form of direct cerebral injury
Nonaccidental injury in children
Birth injury
Nontraumatic
Hypoxic ischemic encephalopathy
Cardiorespiratory arrest
Perinatal asphyxia
Pulmonary disease
Prolonged hypotensive episode
Near-drowning
Suffocation or strangulation
Cerebrovascular injury
Cerebral hemorrhage
Cerebral infarction
Subarachnoid hemorrhage
CNS infection
Bacterial meningitis
Viral meningoencephalitis
Brain abscess
CNS tumor
CNS toxins or poisoning
Degenerative and metabolic disorders
In adults
Alzheimer's disease
Multi-infarct dementia
Pick's disease
Creutzfeldt–Jakob disease
Parkinson's disease
Huntington's disease
In children
Ganglioside storage disease
Adrenoleukodystrophy
Neuronal ceroid lipofuscinosis
Organic aciduria
Mitochondrial encephalopathy
Gray-matter degenerative disorders
Developmental malformations
Anencephaly
Hydranencephaly
Lissencephaly
Holoprosencephaly
Encephalocele
Schizencephaly
Congenital hydrocephalus
Severe microcephaly

*Includes only the most common disorders that have been reported to cause a persistent vegetative state in each of the three categories. CNS denotes central nervous system.

Causes and Clinical Course

The clinical course of a persistent vegetative state depends on the particular underlying disease process.

Acute Traumatic and Nontraumatic Injuries

The most common acute causes of the vegetative state in adults and children are head trauma and hypoxic–ischemic encephalopathy (Table 2). The clinical course after the acute insult usually begins with coma (with eyes closed) for several days to weeks, during which time the acute illness stabilizes and the stunned but ultimately viable brain stem and lower diencephalon resume function.[43-45] By this time, most patients are able to breathe spontaneously and no longer require ventilatory assistance. After the interval of coma, spontaneous opening of the eyes, random eye movements, blinking, and limb movements occur, along with sleep–wake cycles. In a few patients, the vegetative state occurs immediately after the insult, without an initial period of coma.

A persistent vegetative state develops in approximately 1 to 14 percent of patients in prolonged traumatic coma and in 12 percent of those in prolonged nontraumatic coma.[46-51] Although numerous studies have examined a wide variety of clinical and laboratory variables, no well-established criteria applied during the period of coma can, with certainty, predict a vegetative outcome.[52-54] Some evidence suggests a direct correlation between a post-traumatic vegetative outcome and the presence of ventilatory dysfunction, decorticate posturing, and extraneural trauma soon after the insult.[55] Other variables that are correlated with a poor outcome include an advanced age, pupillary abnormalities, and a low score on a test of motor responses.[47] In patients with nontraumatic coma, impairment of eye opening, the presence of abnormal oculocephalic or motor responses, and the inability to obey commands at two weeks are all correlated with a vegetative outcome.[56]

Degenerative and Metabolic Disorders

Many degenerative and metabolic nervous system disorders in adults and children inevitably progress to an irreversible vegetative state. The early stages of such disorders are marked by progressive impairment of intellect, memory, language, motor skills, and social behavior, yet many patients retain some degree of awareness of themselves and their environment. In later stages, awareness disappears, marking the start of a vegetative state.

In patients with degenerative diseases, a persistent vegetative state usually evolves over a period of several months or years.[57] Those who remain in a vegetative state may die of a superimposed infectious illness. Those who survive such an illness remain in a vegetative state or go into a coma. Patients with degenerative diseases who have severe impairment but retain some degree of awareness may lapse briefly into a vegetative state from the effects of medication, infection, superimposed medical or surgical illnesses, seizure activity, or decreased fluid and nutritional intake.[57] The possibility of such a temporary metabolic or toxic encephalopathy must be eliminated before establishing that the patient is in a persistent vegetative state.[21]

Developmental Malformations

Severe congenital malformations of the nervous system in infants and children may prevent the development of awareness or cognition. Among the malformations associated with the developmental vegetative state are anencephaly and hydranencephaly (Table 2). Diagnosis of the vegetative state in infants and children poses several problems related to the immaturity of the developing brain and the ongoing influences of development on the potential for reorganization of structure and function.[58]

On the basis of our understanding of development, the diagnosis of the vegetative state may be difficult to make in infants younger than three months, except in the case of infants with anencephaly. Newborns and young infants have a limited ability to show higher cognitive functions before this age.[59,60] Although they are capable of a variety of social responses, including visual and auditory orientation, cuddling, the ability to be consoled, and self-quieting behavior, these responses may be tenuous, inconsistent, and unsustained until three months of age.[61,62] The concept of the vegetative state cannot be applied to preterm infants because of developmental immaturity and, to a lesser extent, the lack of consistently recognizable sleep–wake cycles.[63,64]

Recognition of the vegetative state in infants and young children also depends on the ability to distinguish between voluntary and involuntary responses.[65,66] Differentiation of voluntary from involuntary responses may be unreliable until approximately three months of age. Voluntary behavior that can be elicited includes a consistent and sustained response of turning to or following visual or auditory stimuli, a growing awareness of social stimuli, cuddling in response to interactions experienced as comforting, and a preference for a specific behavior when several choices are presented. Involuntary behavior includes blinking or wandering, nonpurposeful eye movements; nonspecific sounds and grimace-like expressions in reaction to noxious stimuli; and primitive reflexes, including grasp, postural, startle, and alerting responses.

Some newborn infants with severe developmental malformations, such as hydranencephaly, have a minimal cerebral cortex or none. Such infants usually remain in a developmental vegetative state. Because some brain tissue is developing, these infants may have a limited awareness of their environment and minimal purposeful motor activity within the first several months of life.[67,68] However, only limited improvement has been reported in such children. Those with less extensive malformations (such as certain types of holoprosencephaly or lissencephaly) may appear to be in a vegetative state as infants but eventually show some evidence of awareness and responsiveness. Such infants generally continue to have severe disabilities. There are few reports describing the clinical course of such patients, but some degree of consciousness may emerge.

Pathologic Features

The anatomical basis for a persistent vegetative state differs somewhat from case to case, for several reasons. The interval between brain injury and death affects the nature and severity of pathologic changes. Patients in a vegetative state who die early of medical complications are unlikely to undergo neuropathologic changes that would be sufficient to cause chronic unconsciousness in long-term survivors. Furthermore, in patients with chronic neurologic conditions, other complicating factors, such as severe atherosclerotic disease, may independently injure the brain. In such patients, it may be difficult to determine at autopsy exactly which neuropathologic changes accompanied the initial failure to recover consciousness.

Allowing for the above limitations, two major patterns have characterized most detailed reports on the neuropathology of a persistent vegetative state due to acute traumatic or nontraumatic brain injury. We are not aware of any systematic investigation of the neuropathologic characteristics of patients in whom a persistent vegetative state was due to degenerative, metabolic, or developmental disorders.

Diffuse Laminar Cortical Necrosis

This pattern follows acute, global hypoxia and ischemia. The principal finding is extensive multifocal or diffuse laminar cortical necrosis with almost invariable involvement of the hippocampus. These abnormalities may be accompanied by scattered small areas of infarction or neuronal loss in the deep forebrain nuclei, hypothalamus, or brain stem.[23,69] Relatively selective thalamic necrosis may also follow acute global ischemia, although the specific anatomical boundaries for this uncommon pattern have not been well described[70] (and see the report, elsewhere in this issue of the *Journal*, on studies of the brain of Karen Ann Quinlan).[71]

Diffuse Axonal Injury

This abnormality is usually due to a shearing injury after acute trauma. An extensive subcortical axonal injury virtually isolates the cortex from other parts of the brain.[41] Sometimes a diffuse axonal injury is accompanied by small primary brain-stem injuries, as well as secondary damage to the brain stem that results from transtentorial herniation soon after the injury.[72-74] In patients with an axonal injury complicated by acute circulatory or respiratory failure, diffuse laminar necrosis may also be present.

Only a few pathological reports on the persistent vegetative state describe severe abnormalities of the brain stem. Those that do mainly concern patients in whom severe paramedian mesencephalic damage developed secondary to acute downward or upward transtentorial herniation during the early stage of illness. Lesions confined to the brain stem seldom, if ever, cause long-term unconsciousness, although there has been a report of four patients with severe secondary brain-stem damage in whom coma persisted for as long as six weeks before death.[75] We have found no well-described autopsy studies of patients in a persistent vegetative state who had severe damage confined to the hypothalamus.

Ancillary Diagnostic Studies

Neurodiagnostic tests alone can neither confirm the diagnosis of a vegetative state nor predict the potential for recovery of awareness.[53] However, when used in conjunction with a clinical evaluation, laboratory tests may provide useful supportive information.

Electroencephalography

In most patients in a persistent vegetative state, electroencephalograms (EEGs) show diffuse generalized polymorphic delta or theta activity.[76,77] This pattern is usually not attenuated by sensory stimulation, except occasionally by noxious stimulation.[78,79] In most patients, the transition from wakefulness to sleep is accompanied by some desynchronization of the background activity.[80] In some patients, very-low-voltage EEG activity is all that can be detected. In others, persistent alpha activity is the most remarkable feature. In approximately 10 percent of patients in a vegetative state, the EEG is nearly normal late in the course of illness but without evidence of vision-induced alpha blocking.[77] There have been occasional reports of isoelectric EEGs in patients in a vegetative state.[37,58,76,81,82] Most investigators have not reported this finding, however, nor has it been confirmed by reviews of the initial EEG records by other investigators. Typical epileptiform activity is unusual in patients in a persistent vegetative state, as is seizure activity.

The transition from coma to the vegetative state is not accompanied by notable changes in the EEG. However, clinical recovery from the vegetative state may be paralleled by diminished delta and theta activity and the reappearance of a reactive alpha rhythm.[76,78] This phenomenon is inconsistent and does not predict future recovery.[37,78]

Compressed spectral analysis of the EEG has been used to study patients with prolonged unconsciousness. Preliminary data suggest that patients with changeable or desynchronized spectrograms and abnormal evoked responses remain in a vegetative state.[83]

Infants and children have abnormalities on the EEG that are similar to those reported in adults, although in infants and children the EEG activity may be somewhat more discontinuous and of lower voltage.[66,84]

Evoked-Response Studies

Evoked-response testing is useful statistically, but not always clinically, in trying to assess the risk of a vegetative outcome in patients who are in a coma as a result of an acute neurologic injury.[85] Somatosensory evoked responses are the most sensitive and reliable markers in both adults and children.[86-91] The bilateral absence of such responses one week after the insult is highly predictive of failure to regain consciousness (i.e., of death or survival in a vegetative state). Patients without somatosensory evoked responses, however, may recover at least minimal cognitive activity, especially if the coma is traumatic rather than anoxic.[92,93] In contrast, patients with normal somatosensory responses may enter a vegetative state and remain in it.[88] Prolongation of the central conduction time of an evoked response is a less reliable finding than the absence of a response in predicting a poor outcome.[78,94,95]

Other evoked potentials, such as the brain-stem auditory evoked response, are of limited value. Numerous studies have shown that the brain-stem auditory evoked response is preserved when the somatosensory evoked response is absent, and the outcome is either survival in a vegetative state or death.[78,86,87] Multimodal evoked-response testing may be used to determine the outcome, but whether the results are of greater predictive value than the somatosensory evoked response alone remains uncertain. The presence of P_{300} evoked responses is not necessarily correlated with the outcome.[96]

Neuroimaging

Computed tomographic or magnetic resonance imaging in patients in a persistent vegetative state often reveals diffuse or multifocal cerebral disease involving the gray and white matter. Although there are no established correlations between the results of neuroimaging studies and the development of the vegetative state or the potential for recovery, most patients who do not recover consciousness have abnormal scans.[49,57,67,97,98] When studied during the first several months after a traumatic or nontraumatic brain injury, patients in a persistent vegetative state are more likely to recover consciousness yet remain severely disabled if serial neuroimaging scans are normal than if they are abnormal. Serial scanning usually documents progressive brain atrophy, which reduces the likelihood of neurologic recovery.

Cerebral Metabolic Studies

A substantial reduction in the cerebral metabolic rate has been reported in approximately 20 adults in a persistent vegetative state.[22,99-101] A 40 to 60 percent reduction in global cerebral oxidative metabolism was observed in six patients in a vegetative state after trauma or diffuse anoxia.[99] Positron-emission tomographic (PET) studies showed a 50 to 60 percent decrease in the glucose metabolic rate in the cerebral cortex, basal ganglia, and cerebellum in seven adults; no overlap in metabolic impairment was noted when these patients were compared with three patients who had the locked-in syndrome.[22] Using the same method, other investigators found a 50 percent reduction in cerebral glucose metabolism in patients in a vegetative state, as compared with a 25 percent reduction in metabolic activity in patients who had regained consciousness after anoxic cerebral injuries.[100] The parieto-occipital and mesiofrontal regions had the most consistent reduction in metabolic activity, whereas Levy et al. reported consistently low metabolic rates in all cortical areas.[22]

Although these studies demonstrate substantial reductions in the metabolism of glucose, there is not yet sufficient information to warrant the use of PET scanning to determine prognosis. Likewise, the lack of experience with cerebral metabolic studies in infants and children in a vegetative state precludes the use of such studies to assess prognosis in infants and children. Normal cerebral metabolic activity in this age group is substantially lower than that reported in adults.[102] Questions have been raised about the validity of cerebral metabolic studies to determine whether patients in a vegetative state are conscious or can experience pain and suffering. These questions remain unanswered and require further systematic investigation. Whether patients are conscious and have the potential to experience pain and suffering can best be assessed by careful and repeated neurologic examinations.

Cerebral Blood Flow

Measurement of cerebral blood flow immediately after an acute neurologic injury does not predict a vegetative outcome in either adults or children.[84,103-105] Once a vegetative state exists, however, cerebral blood flow is likely to be reduced. An early study using xenon-133 in four patients in a vegetative state found that cerebral blood flow was 10 to 20 percent of normal.[106] PET studies in seven patients in a persistent vegetative state who were studied 3 weeks to 68 months after acute injury showed a 50 percent decrease in cerebral blood flow.[22] More recent radionuclide-imaging studies using HM-PAO–single-photon-emission computed tomography showed a global reduction in cerebral blood flow 2 to 12 months after a head injury, as well as 3 years later.[107] Some studies, however, have found normal cerebral blood flow in patients in a persistent vegetative state.[108]

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References

1. Jennett B, Plum F. Persistent vegetative state after brain damage: a syndrome in search of a name. Lancet 1972;1:734-7.
2. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Deciding to forego life-sustaining treatment: a report on the ethical, medical, and legal issues in treatment decisions. Washington, D.C.: Government Printing Office, 1983:171-92.
3. Campbell AGM. Children in a persistent vegetative state. BMJ 1984; 289:1022-3.
4. Feinberg WM, Ferry PC. A fate worse than death: the persistent vegetative state in childhood. Am J Dis Child 1984;138:128-30.
5. Cranford RE. The persistent vegetative state: the medical reality (getting the facts straight). Hastings Cent Rep 1988;18:27-32.
6. Spudis EV. The persistent vegetative state — 1990. J Neurol Sci 1991; 102:128-36.
7. Jennett B, Dyer C. Persistent vegetative state and the right to die: the United States and Britain. BMJ 1991;302:1256-8.
8. Position of the American Academy of Neurology on certain aspects of the care and management of the persistent vegetative state patient: adopted by the Executive Board, American Academy of Neurology, April 21, 1988, Cincinnati, Ohio. Neurology 1989;39:125-6.
9. Daroff RB. The American Neurological Association survey results on PVS. Presented at the 115th annual meeting of the American Neurological Association, Atlanta, October 14–17, 1990.
10. Ashwal S, Bale JF Jr, Coulter DL, et al. The persistent vegetative state in children: report of the Child Neurology Society Ethics Committee. Ann Neurol 1992;32:570-6.
11. Council on Scientific Affairs and Council on Ethical and Judicial Affairs. Persistent vegetative state and the decision to withdraw or withhold life support. JAMA 1990;263:426-30.
12. Cantor NL. The permanently unconscious patient, non-feeding and euthanasia. Am J Law Med 1989;15:381-437.
13. Banja JD. Ethical aspects of treatment for coma and the persistent vegetative state. Phys Med Rehabil 1990;4:579-92.
14. Bernat JL. Ethical issues in neurology. In: Joynt RJ, ed. Clinical neurology. Vol. 1. Philadelphia: J.B. Lippincott, 1991:2-57.
15. Tasseau F, Boucand MH, LeGall JR, Verspieren P. États végétatifs chroniques: répercussions humaines aspects médicaux juridiques et éthiques. Rennes, France: Editions École Nationale de La Santé Publique, 1991.

16. Institute of Medical Ethics Working Party on the Ethics of Prolonging Life and Assisting Death. Withdrawal of life-support from patients in a persistent vegetative state. Lancet 1991;337:96-8.
17. Dyer C. BMA examines the persistent vegetative state. BMJ 1992; 305:853-4.
18. ANA Committee on Ethical Affairs. Persistent vegetative state: report of the American Neurological Association Committee on Ethical Affairs. Ann Neurol 1993;33:386-90.
19. American Academy of Pediatrics Task Force on Brain Death in Children. Report of a special Task Force: guidelines for the determination of brain death in children. Pediatrics 1987;80:298-300.
20. The Medical Task Force on Anencephaly. The infant with anencephaly. N Engl J Med 1990;322:669-74.
21. Bernat JL. The boundaries of the persistent vegetative state. J Clin Ethics 1992;3:176-80.
22. Levy DE, Sidtis JJ, Rottenberg DA, et al. Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. Ann Neurol 1987;22:673-82.
23. Dougherty JH Jr, Rawlinson DG, Levy DE, Plum F. Hypoxic-ischemic brain injury and the vegetative state: clinical and neuropathologic correlation. Neurology 1981;31:991-7.
24. Graham DI, McLellan D, Adams JH, Doyle D, Kerr A, Murray LS. The neuropathology of the vegetative state and severe disability after nonmissile head injury. Acta Neurochir Suppl (Wien) 1983;32:65-7.
25. Childs NL, Mercer WN, Childs HW. Accuracy of diagnosis of persistent vegetative state. Neurology 1993;43:1465-7.
26. Celesia GG. Persistent vegetative state. Neurology 1993;43:1457-8.
27. Guidelines for the determination of death: report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. JAMA 1981;246:2184-6.
28. Plum F, Posner JB. The diagnosis of stupor and coma. 3rd ed. Philadelphia: F.A. Davis, 1980.
29. Cranford RE. Neurologic syndromes and prolonged survival: when can artificial nutrition and hydration be forgone? Law Med Health Care 1991;19(1-2):13-22.
30. Ashwal S, Schneider S. Brain death in the newborn. Pediatrics 1989; 84:429-37.
31. Position statement: certain aspects of the care and management of profoundly and irreversibly paralyzed patients with retained consciousness and cognition: report of the Ethics and Humanities Subcommittee of the American Academy of Neurology. Neurology 1993;43:222-3.
32. Dalle OG, Gerstenbrand F, Lücking CF, Peters G, Peters UH. The apallic syndrome. Berlin, Germany: Springer-Verlag, 1977.
33. Minderhoud JM, Braakman R. Het vegeterende bestaan. Ned Tijdschr Geneeskd 1985;129:2385-8.
34. Hellema H. "Life termination" in The Netherlands. BMJ 1991;302:984-5.
35. Sazbon L, Costeff H, Groswasser Z. Epidemiological findings in traumatic post-comatose unawareness. Brain Inj 1992;6:359-62.
36. Brule JF, Danze F, Vallee D. État végétatif: problèmes thérapeutiques. Rev Fr Dommage Corpor 1988;14:191-5.
37. Higashi K, Sakata Y, Hatano M, et al. Epidemiological studies on patients with a persistent vegetative state. J Neurol Neurosurg Psychiatry 1977;40: 876-85.
38. Sato S, Imamura H, Ueki K, et al. Epidemiological survey of vegetative state patients in the Tohoku District, Japan — special reference to the follow-up study after one year. Neurol Med Chir (Tokyo) 1979;19:327-33. (In Japanese.)
39. Tresch DD, Sims FH, Duthie EH, Goldstein MD, Lane PS. Clinical characteristics of patients in the persistent vegetative state. Arch Intern Med 1991;151:930-2.
40. Ashwal S, Eyman RK, Call TL. Life expectancy of children in a persistent vegetative state. Pediatr Neurol 1994;10:27-33.
41. Jennett B. Vegetative state: causes, management, ethical dilemmas. Curr Anaesth Crit Care 1991;2:57-61.
42. Higashi K, Hatano M, Abiko S, et al. Five-year follow-up study of patients with persistent vegetative state. J Neurol Neurosurg Psychiatry 1981; 44:552-4.
43. Levy DE, Knill-Jones RP, Plum F. The vegetative state and its prognosis following nontraumatic coma. Ann N Y Acad Sci 1978;315:293-306.
44. Gillies JD, Seshia SS. Vegetative state following coma in childhood: evolution and outcome. Dev Med Child Neurol 1980;22:642-8.
45. Bricolo A, Turazzi S, Feriotti G. Prolonged posttraumatic unconsciousness: therapeutic assets and liabilities. J Neurosurg 1980;52:625-34.
46. Levy DE, Bates D, Caronna JJ, et al. Prognosis in nontraumatic coma. Ann Intern Med 1981;94:293-301.
47. Braakman R, Jennett WB, Minderhoud JM. Prognosis of the posttraumatic vegetative state. Acta Neurochir (Wien) 1988;95:49-52.
48. Berrol S. Persistent vegetative state. Phys Med Rehabil 1990;4:559-67.
49. Levin HS, Saydjari C, Eisenberg HM, et al. Vegetative state after closed-head injury: a Traumatic Coma Data Bank Report. Arch Neurol 1991;48: 580-5.
50. Sazbon L, Groswasser Z. Outcome in 134 patients with prolonged posttraumatic unawareness: part 1: parameters determining late recovery of consciousness. J Neurosurg 1990;72:75-80.
51. Sazbon L, Zagreba F, Ronen J, Solzi P, Costeff H. Course and outcome of patients in vegetative state of nontraumatic aetiology. J Neurol Neurosurg Psychiatry 1993;56:407-9.
52. Bates D. Defining prognosis in medical coma. J Neurol Neurosurg Psychiatry 1991;54:569-71.
53. Shewmon DA, De Giorgio CM. Early prognosis in anoxic coma: reliability and rationale. Neurol Clin 1989;7:823-43.
54. Childs A. The PLEXUS parameters: results of the 'PLEXUS conference.' Brain Inj 1991;5:73-6.
55. Sazbon L, Fuchs C, Costeff H. Prognosis for recovery from prolonged posttraumatic unawareness: logistic analysis. J Neurol Neurosurg Psychiatry 1991;54:149-52.
56. Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, Plum F. Predicting outcome from hypoxic-ischemic coma. JAMA 1985;253:1420-6.
57. Walshe TM, Leonard C. Persistent vegetative state: extension of the syndrome to include chronic disorders. Arch Neurol 1985;42:1045-7.
58. Ashwal S. The persistent vegetative state in children. In: Fukuyama Y, Suzuki Y, Kamoshita S, Casaer P, eds. Fetal and perinatal neurology. Basel, Switzerland: S. Karger, 1992:357-66.
59. Jones DG. Brain birth and personal identity. J Med Ethics 1989;15:173-8, 185.
60. Korein J. Ontogenesis of the fetal nervous system: the onset of brain life. Transplant Proc 1990;22:982-3.
61. Brazelton TB. Neonatal behavioral assessment scale. Clinics in developmental medicine no. 50. London: Spastics International Medical, 1973.
62. Knobloch H, Stevens F, Malone AF, eds. Gesell and Amatruda's manual of developmental diagnosis: the evaluation and management of normal and abnormal neuropsychologic development in infancy and childhood. 4th ed. Philadelphia: Harper & Row, 1980.
63. Smith SA. Sleep disorders in children. In: Swaiman KF, ed. Pediatric neurology: principles and practice. Vol. 1. St. Louis: C.V. Mosby, 1989: 149-56.
64. Electroencephalography and evoked response. In: Fenichel GM. Neonatal neurology. 3rd ed. New York: Churchill Livingstone, 1990:225-52.
65. Coulter DL. Is the vegetative state recognizable in infants? Med Ethics Physician 1990,5:13-7.
66. *Idem.* The vegetative state in infants: criteria and prognosis. Ann Neurol 1991;30:473. abstract.
67. Aylward GP, Lazzara A, Meyer J. Behavioral and neurological characteristics of a hydranencephalic infant. Dev Med Child Neurol 1978;20:211-7.
68. Shewmon DA, Holmes GL. Brainstem plasticity in congenitally decerebrate children. Brain Dev 1990;12:664. abstract.
69. Ingvar DH, Brun A, Johansson L, Samuelsson SM. Survival after severe cerebral anoxia with destruction of the cerebral cortex: the apallic syndrome. Ann N Y Acad Sci 1978;315:184-214.
70. Relkin NR, Petito CK, Plum F. Coma and the vegetative state associated with thalamic injury after cardiac arrest. Ann Neurol 1990;28:221-2. abstract.
71. Kinney HC, Korein J, Panigrahy A, Dikkes P, Goode R. Neuropathological findings in the brain of Karen Ann Quinlan — the role of the thalamus in the persistent vegetative state. N Engl J Med 1994;330:1469-75.
72. Strich SJ. Diffuse degeneration of the cerebral white matter in severe dementia following head injury. J Neurol Neurosurg Psychiatry 1956;19: 163-85.
73. *Idem.* Shearing of nerve fibres as a cause of brain damage due to head injury: a pathological study of twenty cases. Lancet 1961;2:443-8.
74. Adams JH, Graham DI, Murray LS, Scott LG. Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases. Ann Neurol 1982;12:557-63.
75. McClellan DR, Adams DI, Graham AE, et al. The structural basis of the vegetative state and prolonged coma after non-missile head injury. In: Papo I, Cohadon F, Massarotti M, eds. Le coma tramatique. Padova, Italy: Liviana Editrice, 1986:165-85.
76. Chatrian E. Coma and brain death. In: Daly DD, Pedley TA, eds. Current practice of clinical electroencephalography. 2nd ed. New York: Raven Press, 1990:463-8.
77. Danze F, Brule JF, Haddad K. Chronic vegetative state after severe head injury: clinical study; electrophysiological investigations and CT scan in 15 cases. Neurosurg Rev 1989;12:Suppl 1:477-99.
78. Hansotia PL. Persistent vegetative state: review and report of electrodiagnostic studies in eight cases. Arch Neurol 1985;42:1048-52.
79. Shuttleworth E. Recovery to social and economic independence from prolonged postanoxic vegetative state. Neurology 1983;33:372-4.

80. Oksenberg A, Cohen M, Sazbon L, Becker E. Sleep in prolonged comatose patients. In: Horne J, ed. Sleep '88. Stuttgart, Germany: Gustav Fischer Verlag, 1989:286-8.
81. Mizrahi EM, Pollack MA, Kellaway P. Neocortical death in infants: behavioral, neurologic, and electroencephalographic characteristics. Pediatr Neurol 1985;1:302-5.
82. Brierley JB, Graham DI, Adams JH, Simpson JA. Neocortical death after cardiac arrest: a clinical, neurophysiological, and neuropathological report of two cases. Lancet 1971;2:560-5.
83. Tsubokawa T, Yamamoto T, Katayama Y. Prediction of outcome of prolonged coma caused by brain damage. Brain Inj 1990;4:329-37.
84. Ashwal S, Schneider S, Thompson J. Xenon computed tomography measuring cerebral blood flow in the determination of brain death in children. Ann Neurol 1989;25:539-46.
85. Ahmed I. Use of somatosensory evoked responses in the prediction of outcome from coma. Clin Electroencephalogr 1988;19:78-86.
86. Frank LM, Furgiuele TL, Etheridge JE Jr. Prediction of chronic vegetative state in children using evoked potentials. Neurology 1985;35:931-4.
87. White LE, Frank LM, Furgiuele TL, Montes JE, Etheridge JE. Prognostic value of BAEP with near- and far-field SSEP in childhood coma. Neurology 1985;35:Suppl 1:199. abstract.
88. Brunko E, Zegers de Beyl D. Prognostic value of early cortical somatosensory evoked potentials after resuscitation from cardiac arrest. Electroencephalogr Clin Neurophysiol 1987;66:15-24.
89. Sonnet ML, Perrot D, Bouffard Y, Floret D, Fournet A, Motin J. Les potentiels évoqués somesthésiques et auditifs précoces dans les comas anoxiques: intérêt dans le bilan lésionnel et valeur pronostique. Presse Med 1990;19:166-9.
90. Judson JA, Cant BR, Shaw NA. Early prediction of outcome from cerebral trauma by somatosensory evoked potentials. Crit Care Med 1990;18:363-8.
91. Houlden DA, Li C, Schwartz ML, Katic M. Median nerve somatosensory evoked potentials and the Glasgow Coma Scale as predictors of outcome in comatose patients with head injuries. Neurosurgery 1990;27:701-8.
92. Zegers de Beyl D, Brunko E. Prediction of chronic vegetative state with somatosensory evoked potentials. Neurology 1986;36:134.
93. Tsao CY, Ellingson RJ, Wright FS. Recovery of cognition from persistent vegetative state in a child with normal somatosensory evoked potentials. Clin Electroencephalogr 1991;22:141-3.
94. Hume AL, Cant BR, Shaw NA. Central somatosensory conduction time in comatose patients. Ann Neurol 1979;5:379-84.
95. Lindsay K, Pasaoglu A, Hirst D, Allardyce G, Kennedy I, Teasdale G. Somatosensory and auditory brain stem conduction after head injury: a comparison with clinical features in prediction of outcome. Neurosurgery 1990;26:278-85.
96. Rappaport M, McCandles KL, Rand W, Kraft MC. Passive P_{300} response in traumatic brain injury patients. J Neuropsychiatry Clin Neurosci 1991;3:180-5.
97. Mutoh K, Nakagawa Y, Hojo H. CT appearance of children in a persistent vegetative state. Brain Dev 1987;9:605-9.
98. Coulter DL. Neurologic uncertainty in newborn intensive care. N Engl J Med 1987;316:840-4.
99. Shalit MN, Beller AJ, Feinsod M. Clinical equivalents of cerebral oxygen consumption in coma. Neurology 1972;22:155-60.
100. DeVolder AG, Goffinet AM, Bol A, Michel C, de Barsy T, Laterre C. Brain glucose metabolism in postanoxic syndrome: positron emission tomographic study. Arch Neurol 1990;47:197-204.
101. Momose T, Matsui T, Kosaka N, et al. Effect of cervical spinal cord stimulation (cSCS) on cerebral glucose metabolism and blood flow in a vegetative patient assessed by positron emission tomography (PET) and single photon emission computed tomography (SPECT). Radiat Med 1989;7:243-6.
102. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. Ann Neurol 1987;22:487-97.
103. Jaggi JL, Obrist WD, Gennarelli TA, Langfitt TW. Relationship of early cerebral blood flow and metabolism to outcome in acute head injury. J Neurosurg 1990;72:176-82.
104. Muizelaar JP, Marmarou A, DeSalles AAF, et al. Cerebral blood flow and metabolism in severely head-injured children: part 1: relationship with GCS score, outcome, ICP, and PVI. J Neurosurg 1989;71:63-71.
105. Ashwal S, Schneider S, Tomasi L, Thompson J. Prognostic implications of hyperglycemia and reduced cerebral blood flow in childhood near-drowning. Neurology 1990;40:820-3.
106. Ingvar DH. Cerebral blood flow and metabolism in complete apallic syndromes, in states of severe dementia, and in akinetic mutism. Acta Neurol Scand 1973;49:233-44.
107. Oder W, Goldenberg G, Podreka I, Deecke L. HM-PAO-SPECT in persistent vegetative state after head injury: prognostic indicator of the likelihood of recovery? Intensive Care Med 1991;17:149-53.
108. Agardh CD, Rosen I, Ryding E. Persistent vegetative state with high cerebral blood flow following profound hypoglycemia. Ann Neurol 1983;14:482-6.