Brain Death and the Persistent Vegetative State: Similarities and Contrasts

Bryan Young, Warren Blume and Abbyann Lynch

ABSTRACT: Brain death and the persistent vegetative state (PVS) share the following features: 1.) There is death of neurons in the brain; 2.) Both require an etiology which is capable of causing neuronal death. 3.) The potential for cognition is totally and permanently lost; 4.) Intensive medical support is usually withdrawn. In contrast, the diagnosis of brain death depends on death of the brainstem, while PVS implies permanent and total loss of forebrain function. While brainstem death can be diagnosed clinically, accurate prognosis in PVS requires additional investigation. Thus far, the EEG is the most specific test of neuronal function in the cerebral cortex. Brain death is equivalent to death, while PVS is not; management of the latter is more complex because of medical, social, ethical and legal factors.

RÉSUMÉ: La mort cérébrale et l’état at vegetatif persistant: similitudes et contrastes Les éléments suivants sont communs à la mort cérébrale et à l’état végétatif persistant (PVS): 1) Il y a mort neuronale dans le cerveau. 2) Les deux nécessitent une étiologie capable de causer la mort de neurones. 3) Le potentiel cognitif (individualité) est totalement et irrémédiablement perdu. 4) Les mesures d’appui médical intensives sont habituellement supprimées. Par contre, le diagnostic de mort cérébrale dépend de la mort du tronc cérébral et que le PVS implique une perte totale et permanente de fonction du prosencéphale; la mort du tronc cérébral peut être diagnostiquée cliniquement tandis que pour le PVS, un pronostic exact nécessite une investigation. À date, l’EEG est l’épreuve la plus spécifique de la fonction neuronale du cortex cérébral. La mort cérébrale est équivalente à la mort, alors que le PVS ne l’est pas; la conduite à tenir dans le second cas est plus complexe à cause de facteurs médicaux, sociaux, éthiques et légaux.


Apart from death of the body as a whole, neurological conditions which physicians have accepted as justification for non-initiation or withdrawal of vigorous medical support include brain death and the persistent vegetative state (PVS). Although these entities share several features, there are essential differences. This paper examines the definitions, underlying concepts, criteria and management of each condition. We hope it will stimulate the development of better guidelines for establishing the prognosis and management of patients with severe brain insults.

BRAIN DEATH

Death can be defined as the irreversible loss of function of the organism as a whole.1 In the concept of brain death, then, death of the brain is equivalent to death of the individual.2 Reliable clinical criteria, a standardized set of qualifying conditions and tests, have been developed which, when satisfied, are reliable in assuring that the brain is dead.3 The “physiological kernel” of brain death is death of the brainstem, since its destruction produces the required permanent apneic coma with cranial nerve areflexia.4 If the criteria established in the Guidelines3 are all met, the physician, the family, and society can be assured that no purpose is served by artificially maintaining ventilation and supporting the circulation; that is, in effect, to “ventilate a corpse”.4

The concept that brain death is equivalent with death has allowed the performance of organ transplantation or the termination of support measures.
Intractable coma can only occur if the components of the ascending reticular activating system are irreversibly destroyed, eliminating the possibility of consciousness, arousal and wake-sleep cycles, yet sparing brainstem and diencephalic centres for respirations and homeostatic functions. Intractable coma is extremely rare; sleep-like unarousability almost never persists more than two to four weeks (see below), but evolves into the vegetative state.

Jennett and Plum carefully chose the term “persistent vegetative state” (essentially synonymous but less commonly used labels include coma vigil, akinetic mutism, the apallic syndrome, neocortical death and total dementia) to define a clinical syndrome in which the patient, after initial coma, regains arousability in the sense of eye opening on stimulation. However, there is no evidence of cognition: the individual makes no meaningful interaction with the environment. There is no evidence of recognition. The individual appears incapable of thought, reason, memory, speech, affect or any qualities which are conventionally characteristic of human nature or personhood. There is typically a return of wake and sleep cycles, which, like arousability, depend upon a functioning diencephalon and brainstem tegmentum. The patient may have wandering, conjugate eye movements, but sustained visual pursuit does not occur.

In contrast with brainstem death, PVS is associated with severe and irreversible damage to the cerebrum with or without the diencephalon, while many brainstem functions, such as breathing, chewing, swallowing and cranial nerve reflexes, are largely preserved.

The prevalence of the persistent vegetative state in the United States is conservatively estimated to be between 5,000 to 10,000; this is expected to increase with time. It is, thus, a significant medical and social problem.

**Prognosis of the Persistent Vegetative State**

Some individuals have recovered cognitive function several months or more after a clinical diagnosis of PVS was made. Because of the management implications of the diagnosis of PVS, it is vital that the prognosis be accurately established. Guidelines must be set to identify those who have no chance of recovery, that is those in a persistent vegetative state. How can the extent and severity of the damage be determined? Assessment is more difficult than in the determination of brain death, in which one assesses well-defined cranial nerve reflexes, respirations and reactivity, all of which are intact in the persistent vegetative state.

A priori, the condition causing this syndrome should be capable of destroying forebrain structures to an extent that these structures will have totally and permanently lost their function. Thus, conditions which are by nature potentially reversible, such as many intoxications, hypothermia, sepsis and numerous metabolic conditions (e.g. hypothyroidism, carbon dioxide narcosis and hepatic or renal failure) should be excluded. Examples of diseases associated with or capable of causing permanent structural forebrain destruction include anencephaly and hydranencephaly, in which there is total loss or absence of the telencephalon; large, bilateral cerebral infarctions; hypoxic-ischemic encephalopathy following cardiac arrest; profound hypoglycemia; subarachnoid hemorrhage; “degenerative” diseases such as Alzheimer’s disease; and some infectious and inflammatory diseases of the brain (e.g. Creutzfeldt-Jacob Disease and severe encephalitis). In each of these conditions the extent of the damage must be known to be sufficient to not allow recovery of forebrain function. We wish to emphasize that the diagnosis of these conditions is not, in itself, sufficient to establish the presence of a permanent vegetative state and, thus, to dictate management. It is vital to establish the extent and severity of disease. For example, a dementing individual may have Alzheimer’s disease, but may be far from a permanent vegetative state.

The following approaches are considered:

**The Behavioral (Clinical) Approach**

Clinically, the patient with permanent vegetative state should not show a more complex response than simple eye opening, randomly looking about or blinking to threat or loud noises. There should be no behavioral phenomena that we associate with cognition, such as speech or response to commands. The recognition of the syndrome is not difficult, but how can we determine the extent and permanency of the forebrain damage?

A number of prospective clinical studies have established features which, taken together, allow some prediction of “good” and “poor” outcomes in traumatic and non-traumatic coma. Poor outcomes are mainly equated with little or no likelihood of independent existence. Using various clinical algorithms the prediction of full recovery or severe incapacitation has been achieved with better than eighty per cent reliability in several conditions. However, reliable early clinical predictors that the vegetative state is permanent have not been established. "Poor outcome" patients are heterogenous groups with severe neurological disabilities; these classifications are not equivalent to the permanent vegetative state. Accurate prediction of PVS should be our object in these “survivors”. In subsequent paragraphs, the difficulty in assessment of cerebral cortical function, especially in the absence of response, is discussed.

What is cognition? Cognitive ability includes awareness of oneself, including one’s own mental activity, and the environment. The cognitive process is often tested by the response to a command: the command is interpreted and this information is transferred to the planning and motor systems of the brain which execute the response. (Other sensory modalities including visual, olfactory, gustatory and somatosensory can and perhaps should be used, as long as it is obvious that the patient can respond in a manner that indicates higher order recognition — e.g. removing a noxious stimulus). Skulsky argues that we should also consider the general “activation” of the cerebral hemispheres by the ascending reticular activating system, which also receives the sensory stimulus. Cognition involves perception, higher order information processing, including integration with memory and emotions, as well as generation of ideas and plans. The transformation, reduction, elaboration, storage, recovery and use of information, including previous knowledge, can take place even in the absence of continued stimulation.

How can we clinically exclude cognition or the potential for cognition? Even if there is no obvious relatively selective, severe dysfunction of the “efferent” or motor system, such as
profound extra-pyramidal rigidity, locked-in syndrome or dys-
function of the lower motor units, our clinical study of behavior
is at least a step away from studying perception and cognition:
thought processes can go on without outward behavioral mani-
festations. It is possible to determine that an individual is capa-
bility of thought if he responds purposefully to stimulation, but we
cannot conclusively demonstrate that cognitive processes are not
going on in the absence of such behavior.

The above-mentioned clinical studies provide only an indi-
direct assessment of the severity of the cerebral insult; for exam-
ple, in one of the best studies in predicting responsive awaken-
ing after cardiac arrest,25 the predictive variables were: motor
response, pupillary light reflex, spontaneous eye movements
and serum glucose under 300 mg per deciliter. The major diffi-
culty is that we cannot, in the absence of motor response, clini-
cally study the function of the large regions of the cerebral
hemispheres where integration of sensory information, compre-
hension, generation of ideas and planning take place. We cannot
clinically determine, in any direct manner, how completely or
permanently they have been destroyed.

Thought, at its most basic level, is obvious only to the indi-
vidual; clinically, we cannot adequately assess the dysfunction
of this most highly prized brain activity.

Investigative Tests

By which other methods can we assess the extent of damage
to the cerebral cortex or its connections, which is/are essential
for cognitive processes?28 This cannot be adequately assessed
clinically in the early part of the illness. To determine that the
cerebral cortex has been totally, or essentially totally, and per-
manently rendered incapable of function we have to go beyond
the clinical assessment, by the use of technologically sophisti-
cated investigation.

Such investigative tests cannot directly examine thought, but
they can assess its physiological basis, namely the function of
the neurons in the cerebral cortex, as well as the gross structure
of the cerebrum. Cerebral function can be assessed electrophysi-
ologically, by blood flow determinations and by metabolic stud-
ies, while structure can be assessed by neuro-imaging tech-
niques.

Brain death is the product of technological advancement,
since its existence depends upon intensive care units with venti-
lators and methods of assisting circulation and treating complica-
tions. However, the diagnosis of brain death is dependent on
clinical evaluation; specialized, “high tech” investigations are
usually not required.3 In contrast, PVS is not always dependent
on technology for its occurrence, yet the use of investigative
equipment is necessary for its accurate prognosis.

Electroencephalography

As Pallis4 points out, the electroencephalogram (EEG) is not
a good test for brain death, because it does not assess the brain-
stem, loss of function of which is the essential feature of brain
death. However, the EEG is a good test of cerebral cortical func-
tion. Its physiological basis is the summed synaptic potentials
of neurons, with glia playing only a passive, amplifying role
secondary to neuronal activity.29

There is now reliable information regarding the prognostic
significance of certain EEG patterns in hypoxic-ischemic encephalopathy after cardiac arrest. Binnie et al30 showed that
outcome after cardiac arrest could be predicted by EEG alone in
92 of their 93 recordings with a confidence level of better than
99 per cent. Recordings performed 24-48 hours after cardiac
arrest which show the following patterns have predictive value
for failure to recover behavioral consciousness: iso-electric or
burst-suppression 31-40 or generalized, periodic sharp waves at
intervals of 0.5-2.0 seconds with a suppressed background, usu-
ally in association with myoclonus.30,41,42,43 The iso-electric EEG
(with no signals over 2 microvolts) is probably of greater
predictive value than the others mentioned.32,44 Predictive value
for other patterns is enhanced if a deterioration, e.g. burst-sup-
pression to complete suppression, is found on serial record-
ings.34

Some patterns after cardiac arrest are usually, but not always,
associated with an outcome no better than a permanent vegeta-
tive state. They are, therefore, not as definitive as those showing
complete suppression: generalized epileptiform discharges such
as groups of spikes or continuous spike-and-wave; alpha or
theta coma pattern; persistent, diffuse, unreactive, low-ampli-
tude, irregular delta activity.30,33,45-49 Patients with these patterns
should have serial recordings, as a more prognostically
definitive pattern often evolves within several days of the first
tracing.35,47

Precautions are necessary when the EEG is used to predict
outcome following cardiac arrest. There is a report of recovery
of a patient after electroencephalogram silence lasting up to one hour
when recorded immediately after cardiac arrest;39 one patient,
whose burst-suppression pattern was recorded within 24 hours
post-arrest, recovered.32 In the burst-suppression pattern, the
suppression between bursts should be complete43 and longer
than one second.35 Prediction of outcome using the EEG should
await two or more recordings done more than 24 hours from the
time of cardiac arrest. Patients should be normotensive and
normothermic when recorded and they should not have anesthetic
doses of medication, serious metabolic derangement, sepsis or
active central nervous system disease other than the anoxic-
ischemic insult.

The EEG has not been adequately evaluated as a prognostic
test in other conditions which are capable of causing the perma-
nent vegetative state. It will likely be more useful in those con-
ditions causing neuronal death in the cerebral cortex (e.g.
Creutzfeldt-Jakob disease) than in disorders associated with dis-
connections (e.g. trauma).

Cortical event-related potentials, an extension of EEG, hold
promise as a means of assessing cerebral function. For example,
bilateral absence of cortical (N19-P22) somatosensory evoked
responses has predictive value for death or PVS.30 Further stud-
ies are needed, however, and the procedures require better stan-
dardization before they can be generally applied. It also remains
to be seen whether such tests, which likely co-vary with the
EEG, are superior to the latter.

Cerebral Blood Flow and Metabolic Studies

Regional cerebral blood flow (rCBF) scans and measure-
ments of regional glucose (rCMRGlc) and oxygen metabolism
(rCMRO2) using positron emission tomography (PET), like the
EEG, are tests of function. Timing is important with rCBF:
shortly after coma onset, scans show marked variability.31 Later
in the persistent vegetative state there is usually a reduction in
these activities in the forebrain, but considerable inter-individual
variation persists. Measurements of global cerebral oxygen metabolism and CMRGlc are reduced to about 40-60 per cent of normal in the persistent vegetative state. A concern is that neuronal metabolism probably accounts for only about 50-65 per cent of normal brain oxygen and glucose utilization. Thus, these measures lack the specificity of the EEG, which more specifically reflects neuronal activity. Although it is speculated that the above reduction in these functions represents selective neuronal damage, can this be assumed in the individual case? Although these tests assist the study of such patients and help in the differential diagnosis of the locked-in syndrome, they are available in a small number of centres and are not well standardized. Thus, they seem of little practical value.

There is some promise in a newer technique which uses complex, lipophilic molecules coupled to radioisotopes, such as hexamethylpropyleneamineoxime (HMPAO). These compounds show a high penetration into the brain parenchyma in the first pass through the brain capillaries. The compound changes its steric configuration once in the brain, preventing diffusion back into the blood. The concentration of the compound in the brain, as reflected by the regional changes in radioactivity, is determined by regional cerebral blood flow which, in turn, is dependent on regional metabolic activity. The widespread availability of such agents along with imaging technology, especially single photon emission computerized tomography (SPECT), is an imminent reality. Further improvements in the labelled compound and in imaging may lead to a more reliable test of cortical function. The same theoretical limitations as with rCBF, rCMRGlc and rCMR02 apply, however. Further longitudinal studies are needed to determine outcome and pathological correlation.

Cerebrospinal fluid levels of lactate, glutathione and adenylate kinase have been measured after cardiac arrest. Lactate and/or glutathione levels at 24 and 48 hours, respectively, were significantly higher in those who died early than in longer survivors. These should be studied in PVS, but the large variation of values in the published study is discouraging that these tests will be very useful.

**Neuro-Imaging**

Use of the CT scan and MRI to assess the structural integrity of the brain has obvious attraction. Shortly after an anoxic-ischemic insult, a variety of changes may occur including effacement of cortical sulci, loss of grey-white differentiation, basal ganglia lesions or selective enhancement of the cerebral cortex, basal ganglia or both. Thus far, these early findings have not been of proven prognostic reliability, but further study is needed. Late changes may prove more definitive, but they would be less clinically valuable.

**Significance and Management of Brain Death and the Persistent Vegetative State**

Brainstem death is equivalent to brain death, which is legally regarded as death of the individual. Neurologically, individuals with the persistent vegetative state are not brainstem dead. Since the brainstem is relatively intact (in contrast to the cerebrum), such individuals maintain vegetative and homeostatic functions such as spontaneous ventilation, coughing, swallowing and regulation of temperature and respiration. No society would consider these individuals as "dead"; the thought of burying or transplanting vital organs from such individuals is morally repugnant. Either course would be regarded as equivalent to homicide. The transplantation of organs from anencephalic infants remains controversial — are they special cases who should be considered separately from other PVS patients? This topic deserves a separate paper for discussion.

It is vital that the diagnosis of intractable coma and permanent vegetative state be accurate. Potential for recovery as in some previous cases of "persistent vegetative state" should be excluded.

Thought is the most highly prized activity of the human brain, as reflected in Descartes' statement, "Cognito, ergo sum" (I think, therefore, I am). Our society has adopted this Cartesian philosophy; cognition is regarded as the essential human quality. When cognitive capacity is totally and forever lost, as in intractable coma and the permanent vegetative state, it is generally agreed that use of intensive care units is not justified to needlessly prolong such a low quality of life. Such an existence serves no purpose to the individual and it places great stresses and burdens on families and society. This position is supported by the recommendations of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research in the United States.

Having stated the above, management of patients with PVS can take different levels of care, depending on known preferences of the patient and family. Advance directives from the patient in the form of previously spoken or written statements should be considered. In addition, or in the absence of advance directives, family preferences should be identified. It should be assured that comfort, dignity and hygiene are maintained. In some situations, e.g. if family members cannot agree, referral for judicial review is necessary. Management of cases of PVS should be regularly reviewed by hospital ethics committees.

**Conclusions and Suggestions**

1. Cognitive function is the most valued human quality; when the potential for cognition is totally and permanently absent, prolonging the existence of the body is not socially desirable or necessary. The only conditions which meet the qualifications for lasting absence of cognitive ability are brain death, intractable coma and the persistent (permanent) vegetative state.

2. Although the diagnosis of PVS is made clinically, determination of the prognosis requires clinical assessment and investigative tests. Establishing irreversibility requires an etiology which is capable of causing structural forebrain damage. To establish that such damage is sufficient to preclude the return of cognitive function, investigative tests should examine the function and structure of the cerebral hemispheres and should be available in most tertiary care referral centres. The EEG is the most specific available test of cortical neuronal function, and has proven prognostic reliability in anoxic-ischemic encephalopathy. Event related potentials hold promise but require further study and standardization of technique. The use of SPECT scans with a special lipophilic agent linked to a radioisotope, such as 99mTc-HMPAO, is an available test of brain function that requires further development and assessment. The CT and MRI scans are suitable tests of structure.
3. Management of brain death and PVS are very different. Patients with brain death are legally dead and their organs can be transplanted if consent is obtained. Those with PVS are not legally dead; after the diagnosis and prognosis are established, the level of care is decided upon using advance directives and family preferences. In some cases hospital ethics committees or the courts may need to decide the level of care.

REFERENCES


57. Kjos BO, Brant-Zawadzki M, Young RG. Early CT findings of global central nervous system hypoperfusion. AJR 1983; 141: 1227-1232.


