THE PERSISTENT VEGETATIVE STATE – GENERAL CONSIDERATIONS

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ABSTRACT

The persistent 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 brainstem autonomic functions. It usually follows the coma and it means that due to extensive and irrevocable brain damage a patients is highly unlikely ever to achieve higher functions above a vegetative state.

This state does not mean that improvement is impossible, but does open the possibility for a judicial request to end life support.

The authors wish to highlight the causes, diagnosis, management and ethical considerations about this condition in our country.

Key words: persistent vegetative state, brainstem, coma

HISTORY

In 1940 Ernst Kretschmer was the first who described this syndrome and called it *apallic Syndrome*. The term *persistent vegetative state* (PVS) was coined in 1972 by Scottish spinal surgeon Bryan Jennett and American neurologist Fred Plum to describe a syndrome that seemed to have been made possible by medicine's increased capacities to keep patients' bodies alive.

DEFINITION

A Multi-Society Task Force, seeking to define a common ground of understanding of what was known, medically, about the condition, admitted from the start that there was a manifest "biologic limitation to the certainty of this definition, since we can only infer the presence or absence of conscious experience in another person."

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 hypothalamic and brainstem autonomic functions (1).

Diagnostic criteria for the vegetative state (US Multi-Society Task Force on Persistent Vegetative State guidelines, 1994): (1)

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, tactile, auditory, or noxious stimuli
3. No evidence of language comprehension or expression
4. Intermittent wakefulness manifested by the presence of the sleep-wake cycles
5. Sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care
6. Bowel and bladder incontinence
7. Variably preserved cranial nerve (corneal, papillary, vestibule-cohlear, oculocephalic) and spinal reflexes.

The diagnosis of persistent vegetative state should be established by a physician who, by reason of training and experience, is competent in neurologic function assessment and diagnosis. Reliable criteria do not exist for making a diagnosis of PVS in infants under 3 months old, except in patients with anencephaly.

There is some issues need further explanation in order to comprehend this complex state in US is use the term "persistent vegetative state" and in the

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UK one use two more precisely defined terms: the continuous vegetative state for the patients in a vegetative state for more than four weeks and the permanent vegetative state in which after comprehensive testing and regular twelve month of observation one state that is impossible that the mental condition will ever improve. While the actual testing criteria for a diagnosis of "permanent" in the UK are quite similar to the criteria for a diagnosis of "persistent" in the US, the semantic difference imparts in UK a legal presumption that is commonly used in court applications for ending life support (2).

Another semantic difference was made by William James in 1890 who defined "consciousness" 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 sub served 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.

CAUSES

There are different causes of PVS(1):

A. Traumatic:
a. Non-accidental injury
b. Birth injury
c. Other forms of direct cerebral injury
d. Motor vehicle accidents

B. Non-traumatic:
a. Hypoxic-ischemic encephalopathy:
i. Cardiorespiratory arrest
ii. Near drawninig
iii. Suffocation/strangulation
iv. Arrhythmia
b. Cerebrovascular (Vascular pressure which causes intracranial hemorrhaging or stroke, or infarction)
c. CNS infection (bacterial, viral or fungal infection including meningitis, brain abscess, systemic infections, sepsis)
d. Expansive intracranial processes (tumors, abscess)
e. Toxins (ethanol, atropine, opiates, lead, colloidal silver)
f. Degenerative and metabolic brain disorders (urea cycle disorders, Reye syndrome, ganglioside storage diseases, mitochondrial encephalopathies, hepatic encephalopathy)
g. Electrolyte imbalance (hyponatremia, hypernatremia, hypomagnesemia, hypoglycemia, hyperglycemia, hypercalcemia, and hypocalcemia)
h. Seizure, both nonconvulsive status epilepticus and postconvulsive state (postictal state)
i. Psychogenic
j. severe congenital abnormalities of the central nervous system (anencephaly, hidranencephaly, lissencephaly, severe microcephaly)

DIAGNOSIS

PVS can be diagnosed on clinical ground with a high degree of medical certainty in most adult and pediatric patients after careful, repeated neurologic examinations.

Despite converging agreement about the definition of persistent vegetative state, recent reports have raised concerns about the accuracy of diagnosis in some patients, and the extent to which, in a selection of cases, residual cognitive functions may remain undetected and patients are diagnosed as being in a persistent vegetative state. Objective assessment of residual cognitive functions can be extremely difficult as motor responses may be minimal, inconsistent and difficult to document in many patients, or may be undetectable in others because no cognitive output is possible (2).

The clinical criteria for PVS were underlined in definition. Ancillary neurodiagnostic tests alone can neither confirm the diagnosis of vegetative state nor predict the potential for recovery, but when used in conjunction with a clinical evaluation, laboratory tests may provide useful supportive information:

Electroencephalography: in most patients in PVS EEG shows diffuse generalized polymorphic delta or theta activity (3). This pattern is usually not attenuated by sensory stimulation, except occasionally by noxious stimulation; the transition from wakefulness to sleep is accompanied by some desynchronization of the background activity. The transitions from coma to the PVS is not accompanied by notable changes in the EEG. However clin-

ical recovery from the vegetative state maybe paralleled by diminished delta and theta activity and the reappearance of a reactive alpha rhythm, but this phenomenon is inconsistent and does not predict future recovery (4, 5).

Evoked – response studies: somatosensory evoked responses are the most sensitive and reliable markers in both adult and children (6-9). The bilateral absence of such responses one week after the insult is highly predictive of failure to regain consciousness. Other evoked potentials, such as the brainstem auditory evoked response, are of limited value.

Neuroimaging: CT cerebral or MRI in patients in a PVS often reveals diffuse or multifocal cerebral disease involving the gray and white matter. Serial scanning usually documents progressive brain atrophy, which reduces the likelihood of neurologic recovery (10-12).

Cerebral metabolic studies: a substantial reduction in the cerebral metabolic rate has been reported in adults in PVS. Positron emission tomographic studies (PET) showed a 50 – 60% decrease in the glucose metabolic rate in the cerebral cortex, basal ganglia, and cerebellum (13); the parieto-occipital and mesiofrontal regions had the most consistent reduction in metabolic activity (14). Although these studies demonstrate substantial reduction in the metabolism of glucose, there is not yet sufficient information to warrant the use of PET scanning to determine prognosis. 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.

DIFFERENTIAL DIAGNOSIS

The three principal serious neurological conditions in which there may be overlap of clinical findings on examination that must be differentiated from PVS included:

1. Coma – is a state of deep, unarousable, sustained pathologic unconsciousness with the eyes closed which results from dysfunction of the ascending reticular activating system either in the brainstem or both cerebral hemispheres; coma ussualy requires the period of unconsciousness to persist for at least one hour to distinguish it from syncope, concussion or other state of transient unconsciousness
2. Brain death – describes the permanent absence of all brain functions, including those of the brainstem; the patients are irreversibly comatose, apneic, and have absent brainstem reflexes, including the loss of all cranial nerves functions.
3. Minimally conscious state is a condition of severely altered consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated:

- Following simple commands
- Gestural or verbal yes/no responses
- Intelligible verbalization
- Purposeful behaviors.

TREATMENT

Neuropharmacological therapy mainly uses activating substances such as tricyclic antidepressants or methylphenidate. Promising results have been reported on dopaminergic drugs, particularly amantadine.

Among the most common medications that improve arousal and attention are:

- *dopaminergic drugs* (bromocriptin, levodopa/carbidopa, amantadine),
- *classic stimulants* (methylphenidate, dextroamphetamine, pemoline),
- *antidepressants* (desipramide, protriptylin) and the
- new-generation drugs of *serotonin specific reuptake inhibitors* (fluoxetine).

The drugs that we commonly use in our unit are levodopa/carbidopa, amantadine, amitriptyline tricyclic antidepressant and methyphenidate.

Imidazopyridine

There is currently limited evidence that the imidazopyridine hypnotic drug zolpidem (Stilnox/Ambien) can have positive behavioral effects in some PVS patients. Additionally, stroke victims and patients with head injuries or brain damage following oxygen deprivation, such as near-drowning victims, have reported significant improvements in speech, motor functions, and concentration after treatment with zolpidem. Clauss and Nel (15) presented 3 patients in VS who showed a clinical improvement after the use of Zolpidem (10 mg/day).

A clinical trial of imidazopyridine involving over 360 PVS patients worldwide is currently underway, and 60% of these patients are showing signs of improvement, although no results have yet been published.

Levodopa/Carbidopa

Levodopa/carbidopa turns into active dopamine in a decarboxylation process (16). Case studies

shows that levodopa increases the chance for recovery in patients in PVS. Data shows that only 6% of adult patients recover after being in a vegetative state for six to twelve months. In a prospective study on eight patients, Krimchansky and collaborators (17) found that all patients in a post-traumatic vegetative state treated with levodopa/carbidopa showed an improvement of consciousness after an average of 13 days treatment, and seven of them became conscious to different degrees after an average of 31 days treatment.

Baclofen

Baclofen may have possible effect of partially regained spinal cord outputs on reactivation of cognition by intrathecal administration

Removal of cold intubated oxygen

Another documented case reports recovery of a small number of patients following the removal of assisted respiration with cold oxygen. The researchers found that in many nursing homes and hospitals unheated oxygen is given to non-responsive patients via tracheal intubation. This bypasses the warming of the upper respiratory tract and causes a chilling of aortic blood and chilling of the brain. The researchers describe a small number of cases in which removal of the chilled oxygen was followed by recovery from the PVS and recommend either warming of oxygen with a heated nebulizer or removal of the assisted oxygen if it is no longer needed. The authors further recommend additional research to determine if this chilling effect may either delay recovery or even may contribute to brain damage.

Bifocal extradural cortical stimulation

Bifocal extradural cortical stimulation is a minimally invasive neurosurgical technique which may improve the recovery in PVS. Recently, Canavero et al. (18) have demonstrated that unilateral, bifocal, extradural cortical stimulation (ECS) could produce a therapeutic result in a patient who had been in posttraumatic VS for a period of 20 months. Canavero et al. (18) chose to stimulate the sulcus (parameters: 8–10 Hz, 65 μs, 11 mA) between the left parietal gyri P1 and P2 and the middle frontal sulcus (F2), including the dorsolateral prefrontal cortex (Brodmann's areas 8 and 46). Simultaneous stimulation of the fronto-parietal "consciousness" network may achieve a marked improvement of the default network of the brain.

COMPLICATIONS

Patients in the vegetative state, especially those in the subacute phase, suffer from a wide variety of complications, including epilepsy, hydrocephalus, motors impairments, pressure sores, cachexia, pyrexia of central origin, dysphagia, and others.

Epilepsy is a common phenomenon in patients with VS (about 50%). The attacks can occur soon after the brain damage or as late epilepsy after the first week.

Hydrocephalus is the most common complication in VS patients, mainly in post-traumatic cases (the reported incidence ranges between 0.7 and 62%). It may be due to the atrophy of the white and gray matter (*ex vacuo* hydrocephalus), to a disruption in the flow of cerebrospinal fluid due to adhesions of the meninges (obstructive hydrocephalus), or to problems of absorption of the cerebrospinal fluid (normopressure hydrocephalus).

The pathology of brain damage leads to disturbances in movement and tone such as spasticity, rigidity, paresis, plegia and motor reactivity, which manifests in uncontrolled movements such as chewing, sucking, scratching and stretching.

Normal breathing rhythms may be observed in the vegetative patient, but they also show signs of periodic respiratory rhythms and central hyperventilation. The latter is the worst prognostic factor. Tracheobronchial infection is also a complication that is unavoidable, especially in patients who have been intubated or have a tracheostomy. Tracheomalacia and tracheoesophageal fistula are also frequently observed. Parenchymal lung infection is the most common complication (37%), while a lung abscess is rare. Fat emboli due to skeletal fractures and thrombotic emboli from the limbs are also founded.

The most common cardiovascular manifestation is the hyperdynamic reactivity to head injury, which is mainly expressed by systemic hypertension with systolic values. Changes in heart rate are mostly tachycardia, although bradycardia may also occur and generally has a worse prognosis.

Gastrointestinal problems are common: hemorrhages of the digestive system (both in the acute stage and in the months and even years following brain damage), gastritis, esophagitis or stomach ulcers. Isolation of the clostidium difficile toxin is also frequently seen in this group of patients.

The formation of new bone affects primarily, but not only, the large joints. It is caused by metaplasia of the periarticular connective tissues into bone tissue. This phenomenon is common and its

occurrence ranges from 11 to 76% in different studies. Most of the studies tried unsuccessfully to deduce the etiology from the epidemiologic data.

LEGAL AND ETHICAL ASPECTS

The diagnosis of persistent or permanent vegetative state raises ethical and legal problems. Strict adherence to the doctrine of the sanctity of life would require doctors to continue to maintain the individual, perhaps for many years. However, few would regard this as an appropriate outcome when the person clearly has no capacity to interact with the environment and has no like likelihood of recovery. Provision of nutrition and hydration in these cases merely prolongs an existence, not a life. Moreover, the health care team and the family will be placed under enormous stress if existence is prolonged in this way. Besides that, the patient is in an undignified position, bereft of consciousness and control. On the other hand, in the faces of accepted morality and medical practice the doctors must continue to offer nutrition and hydration in order to maintain life, even the situation is hopeless and the treatment is futile.

RECOVERY

It is possible for some patients to recover spontaneously from a vegetative state in variable period (usually few weeks) (19). The changes of recovery depend on the extend of injury to the brain and the patient's age (younger patients have a better results). Generally the patients have about fifty percent of recovering consciousness from a PVS in the first six months. After what the longer the period, the lower recovery possibility.

Despite rehabilitation, many patients never progress to the point of being able to take care of themselves.

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