

# Persistent vegetative state in Head injury

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**Abstract:** 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 clinical course and outcome of a persistent vegetative state depend on its cause. Post-traumatic unawareness persisting for more than a month should not be considered an irreversible condition, because an outcome that might be regarded by some as being acceptable is possible even in patients with very severe brain damage. Recovery of consciousness from a posttraumatic persistent vegetative state is unlikely after 12 months in adults and children. For most such patients, life expectancy ranges from 2 to 5 years; survival beyond 10 years is unusual. Corpus callosum and dorsolateral brainstem lesions are highly significant in predicting non-recovery. Long-term prognosis of post-traumatic vegetative state (VS) remains poorly defined. Essential prognostic factors of VS include threat blink reflex presence, ventricular dilatation, brainstem and corpus callosal injury; motor score (Glasgow Coma Score) and presence of spontaneous eye movements.

**Keywords:** persistent vegetative state, diffuse axonal injury, outcome, severe head injury.

## INTRODUCTION

Persistent vegetative state (PVS) is a neurological condition in which a person is in a state of complete unawareness of self and environment. This clinical state is also associated with sleep-wake cycle with either partial or complete preservation of hypothalamic and brainstem function<sup>1-5</sup>. Often, many of the patients in vegetative state show slow improvement over months. Hence, this condition may be considered transient, temporary or permanent<sup>1,6-9</sup>. Vegetative state has been reported even at the end of 6 months<sup>5,10-11</sup>. However, diagnosis of vegetative state after 1 year of injury reflects the real clinical state as there is failure to recover from acute or chronic head injury. Approximately 10-14% of all severe head injury patients develop PVS<sup>6</sup>.

## CHARACTERISATION OF VEGETATIVE STATE

Persistent Vegetative State (PVS) is a rare condition. The clinical criteria for PVS (Table 1) include<sup>1,2</sup>:

- No evidence of awareness of self or environment and no ability to interact.
- Lack of evidence of sustained, reproducible, purposeful or voluntary behavioral response to

tactile, visual, auditory or noxious stimuli

- No evidence of language comprehension or expression.
- Intermittent wakeful response with sleep-wake cycles.
- Sufficient evidence of hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care.
- Bladder and bowel incontinence.
- Variably preserved cranial nerve and spinal reflexes

**Table 1. Criteria for diagnosis of vegetative stage**

1.	No evidence of awareness of self or environment and no ability to interact.
2.	Lack of evidence of sustained, reproducible, purposeful or voluntary behavioural response to textile, visual, auditory or noxious stimuli
3.	No evidence of language comprehension or expression.
4.	Intermittent wakeful response with sleep-awake cycles.
5.	Sufficient evidence of hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care.
6.	Bladder and bowel incontinence.
7.	Variably preserved cranial nerve and spinal reflex

Grossman and Hegel<sup>6</sup> suggested additional criteria to distinguish different subjects of vegetative state. They suggested investigative modalities such as CT, MRI, SPECT and EEG to assess the brain dysfunction. However,

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all above parameters are only relative indicators of limited predictive value. The clinical criterion when existed for at least 12 months following injury, the diagnosis of PVS was tenable<sup>12,13,14</sup>. Large numbers of patients who are diagnosed to be in a vegetative state at 6-8 weeks improve significantly over a period of time<sup>12,15</sup>. Thus, diagnosis of PVS is probably incorrect at 3 or 6 months following trauma (Table 2). Dubroja et al<sup>16</sup> analyzed 19 patients with persisting post-traumatic unawareness (>1 month post injury, Glasgow coma scale of 8 or less) Out of 19 patients, 12 patients (63%) regained consciousness, 11 patients (58%) within the first year and one patient (5%) within the second year. The mean duration of unawareness in the patients who recovered consciousness was 190 (range 62-440) days. In the recovery group, according to the Glasgow Outcome Scale, seven out of 12 patients (58%) were moderately disabled and five (42%) were severely disabled at the time of discharge from rehabilitation. All the 12 patients who regained consciousness live with their families, and none had to be kept in an institution. They concluded that awakening from post-traumatic unawareness is possible after a long period. Post-traumatic unawareness persisting for more than a month should not be considered an irreversible condition, because an outcome that might be regarded by some as being acceptable is possible even in patients with very severe brain damage.

**Table 2. Incidence of vegetative state/ Severely disabled with vegetative**

	Year 1979	No of patients	%
1. Jennett et al <sup>10</sup>	International Coma Data Bank	1000	12
2. Marshall et al <sup>11</sup>	1991, NIH Traumatic Coma Data Bank	746	42
3. Celosia <sup>3</sup>	1996	-	14
4. Heindl and Laub <sup>12</sup>	1996	127 Children	5
5. Kampfl et al <sup>14</sup>	1998	80 in PVS at 6-8 weeks	42 at 1 yr. (50%)

### **PATHOLOGY IN BRAIN AND PATHOGENESIS OF PVS**

Earlier it was presumed that the brainstem injury is the commonest cause of PVS. However, neuropathological data do not substantiate the above hypothesis<sup>17-19</sup>. In a MRI study of 42 patients, Kampfl et al<sup>14</sup> reported DAI with lesions in corpus callosum and dorsolateral brainstem to be the key site in posttraumatic PVS. They also proved that the basal ganglia to be the second most common site of injury in patients with PVS. Kinney et al<sup>18</sup> suggested the

role of thalamus in a patient with posttraumatic coma. Other sites, which are abnormal, leading to vegetative state, are the parahippocampal area and the peduncular lesion of the brainstem. In the MRI study reported by Kampft et al<sup>14</sup>, all 42 vegetative patients had lesions in the corpus callosum. Similar observations were also made by other authors on MRI<sup>20-22</sup> findings in persistent vegetative state patients. Strich first identified lesions of corpus callosum in 1956<sup>21</sup>, as prominent features of DAI. Many of these patients followed by Strich developed severe dementia. In addition to DAI there were deep white matter lesions seen in vegetative patients<sup>14</sup>. Lesions of the basal ganglia or thalamus were reported in 52% and 40% respectively in vegetative patients. In hypoxic-ischemic injury leading to PVS, damage to basal ganglia and thalamus are reported as prominent pathological features in radiological imaging<sup>5, 17-18</sup>. Among the corpus callosum lesions, splenium is the commonest site. Adam et al<sup>23</sup> demonstrated corona radiata, white matter of the frontal and the temporal lobe involvement in DAI patients on neuropathological evaluation. Another characteristic feature of DAI is the focal lesion of the dorsolateral part of the midbrain, which was also recorded in 74% of patients of PVS in MRI, reported by Kamp et al<sup>15</sup>. In addition to above lesions, they reported tegmental lesion in 17 (8-bilateral), periaqueductal injury in 7 patients and ventral midbrain lesions, in 21 patients (Bilateral 14). In 32% patients the midbrain lesions had extended into the pons and in five patients, medullary lesions were noticed, which were exclusively localized to the olives. Thus, neuropathological and neuroradiological studies suggest DAI, involving basal ganglia, midbrain and splenium of corpus callosum, in vast majority of patients with PVS. Overall, histological picture reveals a wide spread hypoxic and ischemic damage<sup>5, 17, 18</sup>.

### **CT AND MRI FINDING IN PVS**

In spite of PVS being a well-known and common entity not much literature is available dealing with CT finding in PVS. However, study by Levin et al reported only supratentorial swelling & midline shift<sup>24</sup>, and in their study brainstem injury was uncommon. MRI is far superior to CT scan in detecting DAI, hemorrhagic and non-hemorrhagic contusions in corpus callosum, inferior aspect of frontal and temporal lobes and in the brainstem<sup>14, 15, 21, 25, 26</sup>. Most frequent lesions are either diffuse and at the microscopic level, secondary to disruption of axons at the time of the trauma, or focal and at macroscopic level, also due to torsion or shearing strains on the corpus callosum. They are associated with diffuse axonal injury of hemispheric and brainstem white matter. Focal macroscopic lesions, sometimes extensive, are encountered in 16-40% of autopsies after fatal head injury. Likewise, MRI allows nowadays showing them in

22-49% of nonfatal head injuries. Such lesions can produce an interhemispheric disconnection syndrome. Focal damage to the corpus callosum seems to be a marker of severe injury, with often long-lasting coma and sometimes transitory vegetative state or mutism. Extension of posterior callosal lesions towards adjacent midline structures, such as the fornix, could contribute to the important memory impairment, which is particularly frequently associated with posttraumatic interhemispheric disconnection syndromes. Moreover, MR imaging shows superior sensitivity in detecting posttraumatic shearing injury in subacute stage of head injury. Due to above reasons, MR considered being more helpful than CT in localizing and characterizing posttraumatic brain lesions. In PVS, CT and MRI have shown widespread lesions in the brain (Table 3). In an MRI study in 42 patients with PSV, Kampfl et al reported DAI as the commonest pathology, followed by dorsolateral brainstem and corpus callosum injury and concluded that corpus callosum and dorsolateral brainstem lesions are highly significant in predicting non-recovery<sup>14,15</sup>. Ganglionic lesions were recorded in 22 patients and thalamic lesion in 17 patients with PVS. Supratentorial ventricular enlargement and cortical atrophy were recorded in 28 and 11 patients respectively, while 19 had brainstem atrophy. Thus, the MR imaging at different intervals has helped in finding out the various brain lesions in patients with PVS, which infact has well correlated with the neuropathological findings. Reider-Groswasser et al<sup>27</sup> correlated finding of 3<sup>rd</sup> ventricle in CT with poor outcome. They reported poor prognosis in patients having third ventricle width of 8 mm, and 11mm distance between septum pellucidum and caudate nucleus (Cerebro ventricular Index).

**Table 3. Pathological finding reported in MRI & CT in-patient with Vegetative State**

	Site of lesion	%
1.	Rostral brainstem	75
2.	Basal ganglia	52
3.	Thalamus	40
4.	Hippocampus	21
5.	Parahippocampal gyrus	45
6.	Cortical contusion	48
7.	Corpus Callosum	70
8.	Corona radiata	56

### TREATMENT OF PERSISTENT VEGETATIVE STATE

Patients with early posttraumatic vegetative state can be seen to have recovery when they are followed longer period.

However, accurate prediction of recovery is not possible, and various clinical and laboratory tests fail to predict the recovery. Traumatic Coma Data Bank was analyzed for outcome at the time of discharge from the hospital and after follow-up intervals ranging up to three years after injury<sup>24</sup>. Of 650 patients with closed-head injury available for analysis, 93 (14%) were discharged in a vegetative state. In comparison with conscious survivors, patients in a vegetative state sustained more severe closed-head injury as reflected by the Glasgow Coma Scale scores and pupillary findings and more frequently had diffuse injury complicated by swelling or shift in midline structures. Of 84 patients in a vegetative state who provided follow-up data, 41% became conscious by 6 months, 52% regained consciousness by 1 year, and 58% recovered consciousness within the 3-year follow-up interval. A logistic regression failed to identify predictors of recovery from the vegetative state<sup>24</sup>.

Treatment with multidisciplinary approach has shown better chance of recovery of patients in vegetative state. No doubt vegetative patients need appropriate medical and nursing care<sup>27, 28</sup>. There is also a great role of family and their educational state. Family members also need counseling. After the acute stage, structured protocol based rehabilitation programme helps in faster recovery. Recently, sensory stimulation has been used, based on hypothesis that these stimulations help in fast recovery<sup>29-34</sup>. Those include electric stimulation of dorsal column<sup>31, 34</sup> and median nerve stimulation<sup>32, 33</sup>. Both Cooper et al<sup>33</sup> and Moriya et al<sup>31</sup> reported improvement in vegetative state following the median nerve stimulation. Recently, deep brain stimulation is also used in patients with PVS<sup>34, 35</sup>. Yamamoto et al<sup>35</sup> reported changes in CSF levels of PGD<sub>2</sub>, PGE<sub>2</sub> and monoamines, following deep brain stimulation, in vegetative patients. Cooper et al<sup>32</sup> studied 25 patients and published the efficacy of median nerve stimulation. Some authors have reported value of musical stimulation in recovery of comatose patients<sup>36, 37</sup>.

### PHARMACOTHERAPY IN PERSISTENT COMA

Recently some drugs have been tried in comatose patients. These include aminergic agents, cholinergic agents<sup>38</sup> and Prostaglandin E<sub>2</sub><sup>39</sup>. Dopaminergic drugs have also been tried<sup>40-43</sup>. They include l- dopa<sup>40, 41</sup>, bromocryptine<sup>41-43</sup>, amphetamine<sup>44</sup> and amantadine<sup>45</sup> and various such drugs. Some authors have tried combination of above drugs in patients in coma. Some reports are available reporting the effect of bromocryptine. These drugs help in synaptic transmission of dopamine receptors. A combination of amantadine and bromocryptine has been shown to increase the release of dopamine. A prospective study of eight

patients aged 25-50 years in vegetative state (VS) of mean duration of 104 days following traumatic brain injury (TBI) was performed by investigating changes of their state of consciousness while they were treated with levodopa/carbidopa<sup>46</sup>. Initial improvement was observed in all patients within a mean of 13 days after onset of treatment. Seven patients recovered consciousness after a mean time of 31 days of treatment. The remaining patient showed only slight improvement to minimally conscious state. The sequence of symptoms leading to recovery was the same in all patients; the first to appear was moving a limb on a request, which appeared at a mean time of 13 days. The authors concluded that gradual increase of dose leads to the appearance of better-organized responses like reacting to more than one command, than opening the mouth and appearance of a reciprocal contact<sup>46</sup>. Pharmacotherapy must be started much before cerebral atrophy, as PVS more than 3 months have considerably decreased CBF and CMRO<sub>2</sub>. Overall, outcome in patients with cerebral atrophy is poor. Overall, there may a role of Pharmacotherapy in treatment of prolonged coma (Table 4).

**Table 4. Points on Pharmacotherapy in PSV**

1.	Pharmacotherapy can be started early
2.	Onset of effects occurs earlier than other therapies
3.	Relatively inexpensive
4.	Side effects are only few and mild
5.	If ineffective can be discontinued promptly
6.	Patients can be selected easily
7.	The present pharmacotherapy is quite useful in facilitating early discharge

## CONCLUSIONS

Persistent vegetative state commonly resulting from diffuse axonal injury is a well-known entity in head injury. Damage to corpus callosum, brainstem and corona radiata is often reported in MRI. Early physiotherapy, sensory stimulations, and various pharmacological agents can reduce the number of vegetative patients. Recently, spinal cord and deep brain stimulation are under trial and have provided some promising results.

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