Case Report

Persistent vegetative state after traumatic brain injury - a case report and review of the literature

Rathor MY[1], Rani MFA[2], Shahrin TCA[3], Hashim HZ[4]

Abstract:

Persistent vegetative state (PVS) is a chronic neurological disorder of consciousness, in which patients appear to be awake, but show no behavioural evidence of awareness. It cannot be diagnosed with certainty and misdiagnosis is very frequent. Its management has become one of the most controversial and emotive issues in medical ethics and medical law over the past few decades. The results of recent neuroimaging studies along with well-documented reports of significant late recovery of some PVS patients have challenged the long-held view that restoration of function in the severely traumatic brain injury (TBI) patients is not possible. Some clinicians believe that PVS is a misused term with the potential consequences of withdrawal and withholding of care, and tendency towards less aggressive management. Further naming these patients as "vegetative" has been misinterpreted by many groups that the patient is no more a human but "vegetable" like. Recently there has been an attempt to replace PVS by new, more appropriate name "Unresponsive Wakefulness Syndrome" (UWS). As opposed to brain death, PVS is not recognized by statute as death in any legal system. The context within which end of life decisions are being made for these patients has led to outrage especially if decisions were made to terminate hydration and nutrition. We present a case of young boy who is in a PVS following TBI with the aim to review some of the contemporary issues regarding their management.

Key words: vegetative state; traumatic brain injury; end of life; withdrawal of artificial nutrition and hydration

DOI: http://dx.doi.org/10.3329/bjms.v13i3.19159
Bangladesh Journal of Medical Science Vol. 13 No. 03 July '14. Page : 358-365

Introduction

Traumatic brain injury (TBI) is the most common cause of death or life-long severe disability worldwide. Progress in medicine, diagnostic neuroimaging, and critical care management has considerably increased the number of patients who survive severe acute TBI that in the past would have died[1]. Typically some of these patients recover from coma within the first few days after the insult, while others take more time and go through different stages before fully or partially recovering awareness e.g., minimally conscious state (MCS), vegetative state (VS) or brain death. During the early stages of recovery, external manifestations may not be immediately apparent and repeated bedside examinations over time are necessary to ensure proper diagnosis. This difficulty is reflected by frequent misdiagnoses of coma, MCS, VS and locked-in syndrome (LIS)[2,3]. Although all of these disorders involve severe alteration of consciousness, there are important clinical differences between them that impact on their management. Their correct diagnosis and management has been the subject of increasing scrutiny over the past few decades[4-6]. Further new technologies, most notably functional magnetic resonance imaging (fMRI) and electrophysiological procedures that have emerged during the last 5 years have raised new questions about the relationship between brain

1. Mohammad Yousuf Rathor, Associate Professor Dept. of Internal Medicine
2. Mohammad Fauzi Abdul Rani, Professor and Dean Faculty of Medicine
3. TCA Shahrin, Assistant Professor Dept of Internal Medicine
4. HZ Hashim, Assistant Professor Dept of Internal Medicine

Correspond to: Mohammad Yousuf Rathor**,** Associate Professor**,** Department of Internal Medicine, Faculty of Medicine, Jalan Hospital Campus, International Islamic University Malaysia**,** 27510 Kuantan, Pahang, Malaysia. Email: drmyrathor@yahoo.com

function and consciousness. The results of these studies, along with well-documented reports of significant late recovery of some persistent vegetative state (PVS) patients, has challenged the long-held view that restoration of function in the severely TBI patients is not possible and that all forms of treatment are futile in these patients. Further naming these patients as “vegetative” has been misinterpreted by many groups that the patient is no more a human but “vegetable” like. We appreciate the recent move to avoid the pejorative medical term "PVS" and replace it by new, more humane and appropriate name "Unresponsive Wakefulness Syndrome"(UWS) [7]. Medical professionals face difficult medical, ethical and social dilemmas in management of these cases.[8] The ethical issues arise from their chronic non-cognitive existence as they depend on others to provide for all their needs, which brings in financial concerns. Conflicts arise when physicians recommend withdrawal of life sustaining treatment (LST) over the objections of surrogates. We present a case of young boy who is in a PVS following TBI and attempt to review the specific ethical aspects of managing these patients. In this paper we will continue to refer 'PVS' because the term is so ingrained in medical and legal terminology, till the consensus on new terminology is reached.

Case Report: A 14 year old Malay male boy, the only child of a single mother who had sent him to JAKIM centre for study was admitted to the surgical intensive care unit at our hospital Tangku Ampuan Afzan (HTAA) on 13-3-2012 after a road traffic accident. He had unremarkable past medical history. On arrival to the emergency department he was comatose, with Glasgow Coma Scale (GCS) of 3/15. Pupils were fixed and dilated. He had hematoma on the left side and back of the skull (pariato-occipital hematoma). He was intubated and resuscitated following which his cardiovascular system resumed activity. A computerized scan of the head was performed which revealed left tempo- parietal subdural haemorrhage and brain swelling. The haematoma was removed and decompression craniotomy and fascio- duraplasty was performed. On day 3 after the accident; the patient started showing spontaneous eye opening. He sometimes seemed to be awake, although his eyes could not follow moving objects and he could not obey simple verbal commands of physicians and nurses. He was able to breathe without mechanical support and his cardiovascular, respiratory, renal, and gastrointestinal functions were sound, but he was doubly incontinent. He could open his eyes to auditory stimuli and his mother claimed that he was communicating with her by eye movements. Further examination by our neurologist revealed that he was in VS. Subsequently he developed increased tone and spasticity in upper limbs and increased tone but no spasticity in lower limbs. He had brisk reflexes and up-going planter reflexes. He was managed with passive physiotherapy and nasogastric (NG) tube feeding. He was discharged home with a diagnosis of PVS on 18-7-2012 with spontaneous breathing and GCS of 10/15 on NG tube feeding tab baclofen 5mg TDS and passive physiotherapy. He was readmitted one week later with respiratory tract infection. As per his mother he developed cough and choking after feeding. While in the hospital he developed sudden desaturation with tachypnea of 34 breaths per minute, temp 38 ^{o} C and Spo_2 78-82%. He was intubated and sedated. Vital signs: BP 138/86, pulse 120, ABG (arterial blood gas) analysis showed type 1 respiratory failure. He was diagnosed of type 1 respiratory failure secondary to aspiration pneumonia with underlying pharyngeal dysphagia. In the ward he developed hypokalemia 2.6 mEq/L and occult gastro-intestinal bleed. Sputum culture and sensitivity grew *pseudomonas aerogenosa*. His condition progressively deteriorated into a state of septic shock. He was put on IV sulperazone 2gm BD, IV esomeprazol 40mg OD and nebulised salbutamol. Mother was told about the poor status of her son and given clear message that her son’s end was imminent. She was consoled that children are pure and innocent, and Paradise was assured to them in the life to come. She consented to do not resuscitate (DNR) her son in case of cardio- respiratory arrest. Due to prolonged ventilation, tracheotomy was suggested and mother consented for it. He responded to treatment and on 19-8-12 his GCS was E4V1M1; eyes were open with blank stare. He was comfortable, a-febrile, BP 110/60, pulse 100/mint. He was able to breathe without mechanical support through tracheotomy. His cardiovascular, respiratory, renal, and gastrointestinal functions were normal, but remained doubly incontinent. He tolerated NG tube feeding. He was discharged home on a Ripple mattress, advised regular chest physiotherapy, and further follow-up at our rehabilitation clinic. As of writing, 8 months after the injury, he had spastic quadriplegia, aphonia, dysphagia, and was fully dependent for activities of daily living (ADL). There was not a smile from the

child though he was seemingly beautiful and cheerful. His mother looked very composed, seemingly oblivious to the fact that her child was in that situation.

Disorders of Consciousness after TBI

There are two stages in TBI, the primary and the secondary. Primary brain injury is caused initially by trauma which occurs in seconds after the accident and gets worse by a second injury which happens in minutes and hours after this, depending on when skilled medical intervention occurs. TBI can cause a wide range of disorders of consciousness which are sometimes difficult to distinguish[2,3]. To help determine the extent of TBI and the chance for regaining consciousness, physicians classify them into one of six abnormal conscious states: stupor, coma, PVS, MCS, LIS and brain dead.

Stupor**:** is an excessively long sleep like state from which a person can be awakened only by vigorous external stimuli like loud noise or painful stimuli. TBI can damage areas of the brain stem that control consciousness.

Coma**:** is a profound state of unconsciousness. The individual is alive but patients show no awareness of themselves or their surroundings and they don't open their eyes either spontaneously or by vigorous stimulation[9]. It is usually caused by either temporary or permanent damage to the reticular system. A patient in coma due to (traumatic or anoxic) brain injury, progresses within 2-4 weeks to one of several conditions including death, VS or the MCS[9,10]. Prognosis among traumatic survivors is better than in anoxic cases[11].

Brain death: is diagnosed on the basis of irreversible loss of all brainstem reflexes. These patients need artificial ventilation to survive since they are unable to breathe spontaneously[12].

Vegetative state**:** is a neurological condition in which patients appear to be awake; with cycles of eye closure and opening resembling those of sleep and waking but there is no behavioural evidence of awareness. They have preserved respiration, digestion and thermoregulation[13]. They may manifest a range of reflex reactions to different stimuli; such as smile, cry, grimace, laugh, utter guttural sounds, shed tears or manifest other facial expressions. They may turn their head and eyes towards new sounds or sights. They can make a range of spontaneous movements including chewing, teeth-grinding and swallowing, but are unable to respond to communication or demonstrate awareness of their environment[10]. A few VS patients can take their nourishment orally but vast majority of them, have gross disturbance of the swallowing mechanism. To the families and inexperienced health care professionals, they often look fairly "normal." Loved ones usually remain optimistic, hoping for improvement, praying for their full recovery. One study of children diagnosed as PVS found that in 12 out of 13 cases (92%) parents felt that the children could recognize voices, and that in 8 (62%) of cases parents felt that the children could make their likes and dislikes known; that is to say, in 92% of cases the parents did not accept the diagnosis of unawareness[14].

The most consistent brain damage in VS is in the sub-cortical white matter of the cerebral hemispheres and thalamic neurons, or the white matter connections between the cortex and thalamus, but brain stem and hypothalamic neurons are spared[15,16]. As there is no diagnostic or laboratory test to diagnose VS per se, it is diagnosed by serial bedside neurobehavioral assessments[17,18]. Errors in diagnosis have occurred because of the inexperience of the examiner, or an insufficient period of observation[14]. The diagnosis of PVS should be established by a physician who is competent in neurologic function assessment and diagnosis. When loss of cognition lasts more than one month, the patient is said to be in a PVS[19]. However many patients improve significantly over a period of time, some to the point of good functional outcome[20,21].

The chances of recovery depend on the cause, extent of brain injury, the patient's age, and time spent in the VS. Younger patients have a better chance of recovery than older patients[1,20]. The prognosis of elderly patients in PVS following cardiac arrest is universally poor, whereas the prognosis of children in PVS following TBI is compatible with recovery. There can never be absolute certainty about this but the longer the duration, the less the chance of eventual recovery. In one study among children in PVS due to TBI, 62% recovered, 18% with a good recovery[14]. Another study of 40 patients in the United Kingdom reported that 43% of those patients diagnosed with PVS were misdiagnosed and another 33% were able to recover whilst the study was

underway[22]. Recently investigators using fMRI have reported that some patients in PVS actually had enough consciousness to respond to verbal instructions. Among 54 diagnosed patients, 5 were apparently able to perform a wilful mental imagery task, and on follow-up testing, one was able to answer basic yes-or-no questions[10]. It seems likely that this technique might play a role in decision-making and may soon be offered as evidence in court proceedings.

PVS that holds for more than one?year after TBI and three months after NTBI is considered "permanent" which implies irreversibility[10]. However the use of this term also remains controversial since patients have recovered consciousness after these cut-offs[22]. Further such nomenclature may only serve to create an environment which does not encourage clinicians to pursue treatments which may ameliorate the condition. A 22-year-old male student in PVS recovered consciousness 19 months after TBI. Further slow recovery of motor and cognitive functions up to a moderate disability was observed over 7 years and now he lives in the community and undertakes ADL independently. He has resumed his previous university studies[23]. Dubroja et al analyzed 19 patients with PVS (>1 month post- injury) out of which, 12 patients (63%) regained consciousness, 11 patients (58%) within the first year and one patient (5%) within the second year. 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 TBI is possible after a long period[24]. In February 2005, Sara Scantlin of Kansas awoke from the "PVS" after 20-year, she had been in since a drunk driver hit her in 1984, when she was only 18 years old[25]. Hence, several international working groups have recommended that the terms persistent and permanent be dropped, and simply define VS by duration and its cause[26].

Minimally conscious state**:** is a condition in which patients appear not only wakeful (like VS patients) but also exhibit inconsistent but reproducible signs of awareness[27,28]. They may follow simple commands, show gestural or verbal yes/no responses regardless of accuracy, and/or may verbalize intelligibly[28]. Differentiating a patient in a PVS from one in a MCS can be challenging, but remains critically important, as MCS patients have a better prognosis[28]. Recent studies have reported that as many as 41% of MCS patients were misdiagnosed as being in a VS[27]. These patients, retain large-scale cortical networks responsible for language processing, despite their inability to communicate reliably[29]. One notable example is Terry Wallis, who in 2003,unexpectedly recovered language and motor abilities 20 years after sustaining a severe TBI and was subsequently found to have evidence of regrowth of brain fibers as revealed by MRI diffusion tensor imaging study[30].

Locked-in syndrome**:** is a condition that superficially resembles patients in VS and may be confused with it. In rare cases, it may be difficult to distinguish a PVS from a severe LIS. These patients are awake and conscious but have no means of producing speech, limb or facial movements due to aphonia and quadriplegia. They communicate through eye movements or blinking[26,27]. The classic syndrome involves damage to corticospinal and corticobulbar pathways in the basis pontis[31]. These patients often have full mental function. Once LIS patients become medically stable, they can live several decades if given appropriate medical/nursing care. It is important to recognise this group of patients since eye-controlled, computer-based communication technology currently allows them to control their environment, use a word processor coupled to a speech synthesizer, and access the worldwide net. Recent surveys show that chronic LIS patients self-report meaningful quality of life and the demand for euthanasia is infrequent[32, 33]. One survey of LIS patients found that self-scored perceptions of well-being and distress were not significantly worse than those of age matched controls[34]. So these surveys contradict the notion of people who assume that the quality of life of these patients is not worth living.

Management: TBI patients are treated in an acute care hospital where the focus is primarily on saving and stabilizing them medically. Once that is achieved, the next focus is on recovery of function to whatever level possible. They are monitored by important predictors of recovery, including recovery of spontaneous motility, eye tracking, oculo-cephalic reflex, and disappearance of oral automatisms. Recent studies indicate that multidisciplinary approach and early rehabilitation can improve their functional motor outcome and help in faster recov-

ery. In principle, it is obligatory to provide them with artificial nutrition and hydration (ANH), usually via a feeding tube and antibiotics as they often get infectious complications like pneumonia, pressure sores and urinary tract infections. Recently, electric stimulation of dorsal column and median nerve has been used, to help in fast recovery[35-37]. Deep brain stimulation is under trial and has provided some promising results[37]. Some pharmacological agents which help in synaptic transmission of dopamine receptors have also been found useful. [38] Some authors have reported value of musical stimulation in their recovery[39, 40]. Stem cell therapy is an emerging therapeutic modality with evidence of significant benefits in preclinical stroke models. According to a study, bone marrow stem cell therapy is safe and effective in PVS patients, through lumbar puncture in the sub acute stage[41].

Once the diagnosis of PVS has been established and there is no demonstrable recovery despite best possible care and early rehabilitation measures over more than twelve months in TBI patients, questions are raised regarding their further active management which calls for extensive resources. With the economic reality that exists in most third world countries, physicians are caught by the divide between what they ought to do and what they can do. Further religious beliefs affect the views of patients and health care professionals, which make the formulation of universal legal and ethical guidelines a challenging task in long term management of these cases. They are discharged to an appropriate medical facility, nursing home, or home care as the case warrants.

We believe that the family's wish to keep a PVS patient alive should be respected in general, but, at the same time, to facilitate appropriate care and avoid inappropriate interventions, health care professionals must share all aspects of the illness with the family in a supportive environment and give them time to come to terms with the emotionally charged decisions they are asked to make for their loved one in PVS. Decisions should focus on better physical, emotional and spiritual care, and by no means any sort of patient abandonment. The intrinsic value and personal dignity of human beings does not change depending on their circumstances. It is permissible for patients either through a prior living will or decisions made by immediate family or surrogate, to refuse any treatment or discontinue it, if treating physicians are of the view that there is little or no hope of recovery. Since TBI patients have no advance directive, the treatment decisions are made by health care professionals or immediate family members/authorized surrogate. The decisions of treatment limitation usually begin with a Do-Not-Resuscitate order (DNR) as it would reduce unnecessary patient suffering and medical care costs. Other decisions range from not to perform surgical procedures, not to start vasoactive drugs, hemo-dialysis or other treatments. This practice arguably allows for physician discretion, and promotes better use of health-care resources. Withdrawal of LST is an area of great difficulty for surrogates and physicians alike. [42] Many clinicians do not like to withdraw ANH in a stable PVS patient, rather than when their condition is complicated by critical illness. The patient's family seldom request to withdraw ANH, but favour limiting unnecessary medical interventions that are disproportionate to the expected outcome and would prolong patients suffering. [43] There is no justification in Islam to end a human life merely because of the family's and patient's suffering, as patience and endurance are highly regarded and rewarded values in Islam. The concept of "quality of life" not worthy of living often imposed by economic, social and psychological pressures does not exist in Islam. Those who argue that the maintenance of these patients is an unacceptable burden on the society, and they should be disposed of abruptly than allowing them to deteriorate gradually, is completely alien to Islam. The physicians should write explicit orders indicating which treatments can be administered and which should be withheld. Barring a mutually acceptable solution, physicians may decide to cede to the wishes of the family/surrogates, or as a last recourse, involve the judicial system to achieve resolution. On the other hand, despite a number of recent legal cases, the physicians are still not obliged to submit to pressure by the patient's relatives, to give treatment which they believe to be futile or against the patients' best interests.

Once these patients are at the brink of death and death is imminent, then it is obligatory to stop the treatment and allow the nature to take its course when three consultant physicians advise to do so. Death is not to be resisted, but rather accepted as part of the overall divine plan. [44]

Conclusion: The management of PVS patients is an extremely difficult and challenging task for rela-

tives, medical professionals and society in general. As medical technology advances at a rapid pace, the ability to sustain such patients will improve. Clinical research is needed to continue efforts at researching better ways to manage such patients, and explore novel treatment to facilitate emergence from VS. The stem-cell therapy remains within the experimental arena for the foreseeable future. We need much more data before we make any assertive conclusions about the effect of pharmacological and non-pharmacological treatment in PVS patients. Under current prevailing conditions, when we are facing escalating health care costs particularly in scarce resource communities, we must establish just mechanisms to deal with these patients and limit the use of expensive treatments of marginal benefit, so that that family can achieve an outcome which, however painful, is compassionate.

Ethical approval: Ethics Committee of International Islamic University Malaysia approved publication of this case report.

References:

1. Rickels E, von Wild K, Wenzlaff P. Head injury in Germany – a population-based prospective study on epidemiology, causes, treatment and outcome of all degrees of head-injury severity in two distinct areas. *Brain Inj.* 2010; **24**(12):1491–1504. http://dx.doi.org/10.3109/02699052.2010.498006

2. Childs NL, Mercer WN, Childs HW. Accuracy of diagnosis of persistent vegetative state. *Neurol* 1993; **43**: 1465-67. http://dx.doi.org/10.1212/WNL.43.8.1465

3. Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *BMJ* 1996; **313**:13-16. http://dx.doi.org/10.1136/bmj.313.7048.13

4. Klaus R.H. von Wild. Neurorehabilitation following craniocerebral trauma. *European. J of Trauma*. 2005; **4**: 344 – 58. http://dx.doi.org/10.1007/s00068-005-2059-z

5. Laureys S. Permanent vegetative state and persistent vegetative state are not interchangeable terms. *BMJ*. 2000 Available from: http://bmj.com/cgi/eletters/321/7266/916#10276.

6. Shewmon DA. A critical analysis of conceptual domains of the vegetative state: sorting fact from fancy. *Neuro Rehabilitation*. 2004; **19**:343–47.

7. Laureys S, Celesia GG, Cohadon F. The European Task Force on Disorders of Consciousness. Unresponsive wakefulness syndrome: a new name or the vegetative state or apallic syndrome. *BMC Medicine*. 2010; **8**: 68 – 71. http://dx.doi.org/10.1186/1741-7015-8-68

8. Machado C. Brain Death: A reappraisal. *New York: Springer*. 2007;121–6.

9. Plum F, Posner JB. The diagnosis of stupor and coma. Philadelphia*: F.A. Davis Co*., 1983;**3**: 363-4.

10. Anonymous: Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. *N. Engl. J. Med*. 1994; **330**: 1499-508. http://dx.doi.org/10.1056/NEJM199405263302107

11. Laureys S, Owen AM and Schiff ND: Brain function in coma, vegetative state, and related disorders. *Lancet Neurol*. 2004; **3**: 537-46. http://dx.doi.org/10.1016/S1474-4422(04)00852-X

12. Goila AK. The diagnosis of brain death. *Indian J Crit Care Med*. 2009; **13**(1): 7–11. http://dx.doi.org/10.4103/0972-5229.53108

13. Monti MM, Laureys S, Owen AM. The vegetative state *BMJ* 2010; **341**:c3765. http://dx.doi.org/10.1136/bmj.c3765

14. Fields, A., Coble, D., Pollack, M., Cuerdon, T., & Kaufman, J. Outcomes of children in a persistent vegetative state, Critical Care Medicine, 1993; **21**(12): 1890-94. http://dx.doi.org/10.1097/00003246-199312000-00016

15. Celesia GG: Persistent Vegetative state. *Neurology* 1993; **43**: 1457-8. http://dx.doi.org/10.1212/WNL.43.8.1457

16. Kenard C, Illingworth R. Persistent Vegetative State. *J Neurol Neurosurg Psychiat* 1995; **59**: 347-55. http://dx.doi.org/10.1136/jnnp.59.4.347

17. Giacino JT, Zasler ND, Whyte J, Katz DI, Glenn M, Andary M. "Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness," *Archives of Physical Medicine and Rehabilitation*.1995; **76**: 205-9. http://dx.doi.org/10.1016/S0003-9993(95)80031-X

18. Giacino JT & Zasler ND. "Outcome following severe brain injury: the comatose, vegetative and minimally responsive patient," *Journal of Head Trauma Rehabilitation*. 1995; **10**(1):40-56. http://dx.doi.org/10.1097/00001199-199502000-00006

19. Jennett B & Plum F. "Persistent vegetative state after brain damage: a syndrome looking for a name.*"* *Lancet*. 1972; **1**:734-37. http://dx.doi.org/10.1016/S0140-6736(72)90242-5

20. Heindl UT, Laub MC. Outcome of persistent vegetative state following hypoxic or traumatic brain injury in children or adolescents. *Neuropediatrics* 1996; **27**: 94-100. http://dx.doi.org/10.1055/s-2007-973756

21. Kampfl A, Schmutzhard E, Franz G, Pfausler B, Haring HP, Ulmer H, Felber S, Golaszewski S, Aichner F. Prediction of recovery from post-traumatic vegetative state with cerebral MRI. *Lancet* 1998; **35**: 1763-7. http://dx.doi.org/10.1016/S0140-6736(97)10301-4

22. Childs NL and Mercer WN: Brief report: late improvement in consciousness after post-traumatic vegetative state. *N Engl J Med*. 1996; **334** (1): 24-25. http://dx.doi.org/10.1056/NEJM199601043340105

23. Sancisi E, Battistini A, Di Stefano C, Simoncini L, Simoncini L, Montagna P, Piperno R. Late recovery from post-traumatic vegetative state. *Brain Inj*. 2009 ; **23** (2) : 163 - 6. http://dx.doi.org/10.1080/02699050802660446

24. Dubroja I, Valent S, Miklic P, Kesak D. Outcome of posttraumatic unawareness persisting for more than a month. *J Neurol Neurosurg Psychiatry* 1995; **58**:465-6. http://dx.doi.org/10.1136/jnnp.58.4.465

25. Woman Details Her 20-Year Coma," CBS News, Aug. 4, 2005.

26. American congress of Rehabilitation Medicine. Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness. *Arch. Phys. Med. Rehabil*., 1995; **76** : 205-09.

http://dx.doi.org/10.1016/S0003-9993(95)80031-X

27. Schnakers C, Vanhaudenhuyse A, Giacino J, et al. "Diagnostic Accuracy of the Vegetative and Minimally Conscious State: Clinical Consensus versus Standardized Neurobehavioral Assessment.BMC *Neurology* 2009; **9**: 35. http://dx.doi.org/10.1186/1471-2377-9-35

28. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al.: The minimally conscious state: definition and diagnostic criteria. *Neurology*. 2002; **58**: 349-53. http://dx.doi.org/10.1212/WNL.58.3.349

29. Schiff ND, Rodriguez-Moreno D, Kamal A, Kim KHS, Giacino J, Plum F, Hirsch J. Functional MRI reveals large scale network activation in minimally conscious patients. *Neurol,* 2005; **64**:514-23. http://dx.doi.org/10.1212/01.WNL.0000150883.10285.44

30. Voss HU, Uluc AM, Dyke JP, Watts R, Kobylarz EJ, McCandliss BD, et al.: Possible axonal regrowth in late recovery from the minimally conscious state. *J Clin Invest.* 2006; **116**: 2005-11. http://dx.doi.org/10.1172/JCI27021

31. Bruno M, Bernheim JL, Schnakers C and Laureys S: Locked-in: don't judge a book by its cover. *J Neurol Neurosurg Psychiatry*. 2008; **79**: 2. http://dx.doi.org/10.1136/jnnp.2007.125294

32. Laureys S, Boly M, Moonen G and Maquet P: Arousal and awareness in coma and post-comatose states, in Squire EEL: New Encyclopedia of Neuroscience 2008.

33. Tshibanda L, Vanhaudenhuyse A, Galanaud D, Boly M, Laureys S, Puybasset L. Magnetic resonance spectroscopy and diffusion tensor imaging in coma survivors: promises and pitfalls. *Prog Brain Res*. 2009; **177**: 215-29. http://dx.doi.org/10.1016/S0079-6123(09)17715-4

34. Boly M, Faymonville ME, Schnakers C, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. *Lancet Neurol* 2008; **7**: 1013-20. http://dx.doi.org/10.1016/S1474-4422(08)70219-9

35. Yokoyama T, Kamei Y, Shoda M, et al. Treatment of vegetative status with Dorsal Column stimulation. *Neurol Surg (Tokyo*) 1990; **18**: 39-45.

36. Cooper JB, Jane JA, Alves WM, et al. Right median nerve stimulation to hasten awakening from coma. *Brain Injury* 1999**;** **13**: 261-267. http://dx.doi.org/10.1080/026990599121638

37. Matsui T, Fujiwara S, Takahashi H et al. Indication of electrical deep brain or dorsal column stimulation and new scoring system for prolonged impaired consciousness. *J Neurosurg. (Tokyo*) 1998; **7**: 14-23.

38. Krimchansky BZ, Keren O, Sazbon L, Groswasser Z. Differential time and related appearance of signs, indicating improvement in the state of consciousness in vegetative state traumatic brain injury (VS-TBI) patients after initiation of dopamine treatment. *Brain Inj* 2004; **18**:1099-105. http://dx.doi.org/10.1080/02699050310001646206

39. Ueda K, Yanagida M. Effect of music on brain in the unconscious patients. Paper presented at 8th Annual meeting of Society for Treatment of Coma. Beppu, Oita July 30, 1999.

40. Ijichi K, Tsutsu A, Maeda T, et al. Musical exercise therapy for patients with persistent disturbance of consciousness. Presented at the 8th Annual meeting of the Society for treatment of coma. Beppu, Oita July 30, 1999.

41. Tian C, Wang X, Wang X, Wang L, Wang X, Wu S, Wan Z. Autologous Bone Marrow Mesenchymal Stem Cell Therapy in the Sub-acute Stage of Traumatic Brain Injury by Lumbar Puncture. Exp Clin Transplant. 2012. DOI:10.6002/ect.2012.0053 http://dx.doi.org/10.6002/ect.2012.0053

42. Nyman DJ & Sprung CL. End-of-life decision making in the intensive care unit. *Intensive Care Medicine*. 2000; **26**:1414-20. http://dx.doi.org/10.1007/s001340000641

43. Hines S C, Glover J J, Babrow A S, Holley J L, Badzek L A, Moss A H. Improving advance care planning by accommodating family preferences. *Journal of Palliative Medicine.* 2001; **4**: 481-89. http://dx.doi.org/10.1089/109662101753381629

44. Neuberger J. Caring for Dying Patients of DjJerent Faiths,*London: Mosby*, 1994;**2**:36