Recovery From Vegetative State: A Four-Years Follow Up

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Abstract

Although the general observation that the longer the duration of the vegetative state, the lower the probability of emerging from it remains true, reports of late improvement are ever more common in the literature. The aim of this study was to verify evolution from Vegetative State in a group of inpatients in a Neurorehabilitation facility and to identify the parameters increasing the likelihood of transition to a Minimally Conscious State. A retrospective review of 259 patients admitted consecutively suffering the sequelae of a severe brain injury (initial Glasgow Coma Scale ≤ 8) was performed to evaluate course of recovery during hospitalisation and in follow-up, 1-4 years post-injury. In our series of 75 patients admitted in a Vegetative State and undergoing neurorehabilitation, 10 were still in a Vegetative State 36 months after the acute event and were observed until 48 months after their admission to the Vegetative State Unit. In the last 12 months of observation, 2 patients died, 5 remained in a Vegetative State and 3 were showing signs of improved consciousness.Univariate analysis identified the parameters increasing the likelihood of transition to a Minimally Conscious State as male sex, youth, shorter time from the onset of Vegetative Sxtate, presence of widespread injury and presence of status epilepticus.

Introduction

Patients who have suffered severe traumatic or non-traumatic brain injuries can undergo progressive recovery through a wide range of clinical conditions. Although there may be some overlap between these conditions, their severity can vary [1]. These different clinical stages are often described using standardised tools for the evaluation of cognitive state [2, 3] or purely descriptive neurological criteria [4, 5] (**Table 1**).

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Patients may progress from coma to a vegetative state (VS) and/or minimally conscious state (MCS) [6]. While these may be temporary clinical conditions [7], in some cases they represent the stabilised outcome of the acute cerebral event and the patient never recovers full consciousness [8].

Vegetative state, recently described as "unresponsive wakefulness syndrome" [9], involves a disconnection between the thalamus and cerebral cortex [10,11], secondary to a variety of acute events with different causes. These commonly involve diffuse axonal injury caused by traumatic brain injuries (TBI) involving shearing forces [12], hypoxic-ischaemic neuronal damage [13] or cerebral haemorrhage [14] causing injury to the cortex and thalamus.

Minimally conscious state differs from vegetative state through the presence of behaviours demonstrating conscious awareness [15] . Although they may appear inconsistently, they are repeatable and maintained for a sufficient time to enable them to be differentiated from reflexive behaviours [16].

The constant attention to the clinical evolution of patients with consciousness disorders following severe brain injuries has probably modified epidemiological data concerning emergence from VS. Although the general observation that the longer the duration of the VS, the lower the probability of emerging from it remains true, reports of late improvement are ever more common in the literature [17].

The aim of this study was to verify evolution from VS and MCS in a group of inpatients in a neurorehabilitation facility and to establish what prognostic factors might be observed in subjects showing signs of emergence, however late, from VS.

Materials and Methods

Between January 2005 and January 2009, 259 patients suffering the sequelae of a severe brain injury - initial Glasgow Coma Scale (GCS) ≤ 8 - were admitted consecutively to the neurorehabilitation facility at ASL CN1 – Cuneo (Italy). Of these, 75 (28.9%) presented a vegetative state and 107 (41.3%) a minimally conscious state on admission. 56 (74.6%) of the patients initially admitted in a vegetative state did not return to consciousness and were transferred to a specialised slow-to-recover brain injury programme in the Vegetative State Unit (VSU).

The VSU in the Department of Rehabilitative Medicine accepts clinically stabilised patients with a diagnosis of vegetative state secondary to a traumatic brain injury (at least one year after the acute traumatic event) or a non-traumatic brain injury (at least 6 months after the acute haemorrhagic or hypoxic event). The only criterion precluding access to the Unit is mechanical ventilation. Patients with a tracheotomy tube or percutaneous endoscopy gastrostomy (PEG) tube are accepted and there are no time limits with respect to the acute event, although the earliest possible access is guaranteed.

A retrospective review of these cases was performed to evaluate course of recovery during hospitalisation and in follow-up, 1-4 years post-admission to the VSU. There were 33 males (58.9%) and 23 females (41.1%), with a mean age of 25 ± 19 years. Patients were admitted in the late recovery period (mean 42 ± 52 weeks). The causes were as follows: traumatic head injury (n = 15), post-anoxic-ischaemic encephalopathy (n = 27), ischaemic or haemorrhagic stroke (n = 6), aneurysmal subarachnoid haemorrhage (n = 6), and miscellaneous acute neurological conditions (n = 2).

A detailed medical history was collected for all patients. A physical medicine examination and neurological examination were carried out every week and routine blood tests and, where necessary, radiological and neuroradiological investigations were carried out every month.

The VS Unit rehabilitation programme for these patients includes the provision of optimal nutrition, control of infections, management of bladder, bowel and autonomic disorders, provision of specialist seating and control of posture and tone problems. Patients underwent one hour of rehabilitative treatment and speech therapy every day, to prevent tertiary injury. Rehabilitative treatment involved passive joint mobilisation and helping/placing patients into an upright sitting position on a tilt table.

All patients underwent a specific assessment protocol every month to identify any emergence, however late, from the vegetative state. Finally, the Coma Recovery Scale-Revised (CRS-R) was applied [3]; its purpose is to assist differential diagnosis, prognostic assessment and treatment planning in patients with consciousness disorders. It consists of 23 items comprising 6 subscales addressing auditory, visual, motor, oromotor, communication and arousal functions.

The subscales consist of hierarchically-arranged items associated with brain stem, subcortical and cortical processes. CRS-R seems well adapted to reveal emergence from VS and its prognostic utility has been confirmed in many studies, suggesting that is suitable for assessing levels of consciousness and monitoring recovery of neurobehavioral function [18-20].

All patients underwent treatment with amantadine for at least 30 days. All patients were treated with baclofen via PEG tube (dosage between 50 and 75 mg), except for 2 treated with baclofen via an intrathecal delivery system.Levetiracetam was used in 2 patients who had presented tonic-clonic seizures. No cranioplasties or ventricolo-peritoneal shunts were performed in the observation period.

6 months after admission to the VSU, all 56 patients were still in a vegetative state. In the following 6 months, 7 recovered some consciousness, with locked in syndrome diagnosed in two cases and MCS in the 5 others. These patients remain severely disabled and are completely dependent on the help of others for activities of daily life.

37 and 10 patients were still in a VS after 24 months and 36 months respectively. In other words, in our series of 75 patients in VS undergoing neurorehabilitation between January 2005 and January 2009, 10 (13.3%) were still in a VS 36 months after the acute event. 30 patients died, 7 – still in a VS - were discharged to a specialist nursing facility, 2 were discharged home and 26 recovered some consciousness. The outcome of the 9 discharged patients is not known, as they were lost to follow-up. 10 patients (4 men and 6 women - mean age 31.7 ± 7.5 years) remained permanently unconscious and were observed until 48 months after their admission to the VS Unit. In the last 12 months of observation, 2 patients died, 5 remained in a vegetative state and 3 were showing signs of improved consciousness **(Table 2).**

In the statistical analysis, 9 variables were taken into consideration for each patientto establish if any clinical elements might be correlated with recovery: 1) sex, 2) age at onset of coma, 3) time passed since onset of VS, 4) aetiology of the coma (categorised as traumatic brain injury, anoxic encephalopathy, haemorrhagic encephalopathy), 5) CRS-R score on admission to the VS Unit, 6) CRS-R score 48 months after admission to the VS Unit, 7) duration of the coma, 8) injuries revealed on neurological scanning (presence of focal injury, cortical atrophy and/or subcortical atrophy) and 9) late onset of epileptic seizures.The Wilcoxon or Kruskal Wallis tests were used for the univariate analysis, with F distribution for the continuous variables, while Pearson's chi-squared test with Yates' correction for continuity was used for categorical variables, making the test conservative, as with Fisher's exact test. As the caseload was substantially reduced by the deaths of numerous patients, the analysis was carried out having excluded these subjects. Given these limits, the multivariate analysis was carried out only for comparison of MCS and VS.

Results

The mean duration of life in a vegetative state of patients dying during the observation period was 564 days (minimum 275, maximum 1189). 9, 20, and 2 patients died in years 2, 3 and 4 respectively. The cause of death was infectious disease in 18 cases (12 pulmonary), neurological diseases in 7 cases, heart disease in 3 cases and unknown in the 3 others.

Non-TBI patients were followed for an extended time (mean 18 months), beyond the 3-month duration deemed ''permanent''. TBI patients were followed for a mean of 28 months, 16 months more than the 12-month period beyond which recovery from VS is considered very unlikely in such patients.

The clinical and demographic features of the 10 patients followed for 48 months after admission to the VS Unit are described in **Table 3**. Three patients recovered consciousness, transitioning to MCS, 2 died, and 5 remained unconscious. For those who emerged from VS, the mean duration of VS was 46 months.

Univariate analysis identified the parameters increasing the likelihood of transition to a minimally conscious state as male sex, youth, shorter time from the onset of VS, presence of widespread injury and presence of Status Epilepticus (SE) (**Table 4)**. These descriptive observations were reflected in the multivariate model, with a significance level of 10%. The probability was around 3 times higher (OR 0.33) when less than 56 days had elapsed since the onset of VS. Patients suffering seizures were roughly twice as likely to progress to a minimally conscious state as those without seizures, although this was not statistically significant.

Discussion

Although the sample size (10 patients) is large for this specific condition, it is small with respect to the common standards for statistical analysis of a clinical caseload. This study should thus be considered a pilot study of the parameters determining transition to a minimally conscious state. In this case, given the level of significance of 5% (p < 0.05), it could even be a first step towards the formulation of quantitative theories worthy of further research.

VS is a severe neurological syndrome, involving the loss of all types of conscious behaviour despite preserved wakefulness. The transition from VS to MCS is defined by the first signs of minimal, inconsistent, but reproducible behavioural evidence of self- or environmentalawareness, as defined by the Aspen workgroup criteria [15]. The right diagnosis is essential in deciding when and what type of assistance should be provided to the patient over time.

Patients with severe brain injuries, whether traumatic or non-traumatic in origin, often progress from an initial coma towards a vegetative state and subsequently towards a minimally conscious state. However, they do not always achieve full consciousness or self-awareness. Various studies in the literature analyse the probability of emergence from VS, including of over one month's duration [21-24]. Less information is available on the evolution of MCS of over one month's duration [25-27]. The Multi-Society Task Force has formulated several principles. The prognosis for regaining awareness from non-traumatic VS is worse than for an equivalent state following a TBI, and the longer patients remain in a VS, the less likely they are to eventually regain awareness. The Task Force's final conclusion is that late recovery of consciousness - beyond 12 months after onset in TBI and beyond 3 months after onset in non-traumatic injuries - is very unlikely.

The data currently available are insufficient for reliable estimates of the incidence of late improvement, due to sporadic follow-up reports, incomplete epidemiological data and imprecise diagnoses. Late improvement (albeit with persistent severe cognitive impairment) from VS may therefore be more common than thought, and in fact recent articles on patients with acute or post-acute VS report a more favourable long-term prognosis for VS and MCS than in the past [28-32].

Avesani and colleagues stress the importance of constant follow-up in studies involving patients with consciousness disorders, to enable suitable monitoring of any variations in the clinical picture, especially when the baseline condition is particularly severe [33]. They described 2 people diagnosed with VS who, 6 and 12 months respectively after their original trauma, achieved a moderate level of functional independence after significant motor and cognitive recovery. Similarly, Estraneo and colleagues described 6 VS patients who recovered a level of consciousness considerably better than that identified in the Multisociety Task Force prognostic guidelines. This recovery was more evident in younger subjects who had suffered severe TBI [17].

Sancisi and colleagues described the case of a 22-year-old male student who recovered consciousness from a vegetative state 19 months after a traumatic brain injury. In the authors' opinion, cranioplasty and long-term rehabilitation programmes could be among the variables potentially influencing this unexpected recovery [34].

Luauté and colleagues studied the prognosis of VS and MCS over a 5-year observation period. They found no instances of improved awareness in any of the 12 VS patients, all of whom either died or remained in a VS. In contrast, MCS patients showed improvement more than 1 year after the onset of coma [35].

A VS lasting more than 1 year after TBI or 6 months after anoxic/vascular disease used to be considered ''permanent'', which implies irreversibility or the extremely improbability of even a minimal improvement after this period. However, according to studies on late recovery of consciousness - beyond 12 months after onset in TBI or 3 months after onset in non-TBI - some patients may have the potential for noteworthy additional recovery [36-37].

In any case, emergence to a state of more consistent consciousness can take months or even years, in rare cases, and is always associated with severe to extremely severe functional disability and a poor functional outcome.

Figures reported in the literature for late emergence from VS show a large variance, from 1.6% to 14% [29, 38-39]. Data on emergence from MCS are marred by the poor reliability of the prognostic indicators and probably by the different terminological choices used in recent years to define emergence from VS. As with VS, the longer MCS persists, the lower the probability of recovery. In a group of acute TBI patients initially in MCS, 40% will regain full consciousness within 12 weeks of injury, and up to 50% will regain independent function at 1 year [3].

In Luauté and colleagues' study, one-third of the patients in MCS improved after more than a year, though they remained severely or totally disabled [35]. This result has obvious implications for rehabilitation, which could enable further improvement. An age greater than 39 years and the absence of middle-latency auditory evoked potentials were independent early predictors of poor outcome.

Lammi and colleagues found that the recovery of patients after prolonged MCS varied greatly. The duration of the MCS did not seem to influence the psychosocial outcome, nor did it preclude significant functional recovery [40]. Katz and colleagues demonstrated that patients in VS whose transition to MCS occurred within 8 weeks of onset are likely to continue recovering to higher functional levels, with a substantial proportion regaining home independence and productive pursuits. Patients with TBI are more likely to progress than those with non-TBI, though significant improvement in the non-TBI group is still possible [22].

No neurological interpretation of late recovery has been suggested for such cases, and early predictors of the outcome of VS might not apply [41-43].

Taken as a whole, these data confirm that an accurate early diagnosis for patients with consciousness disorders following brain injury is critical for the prediction of outcome. Diagnostic errors are likely to result in the prediction of a worse prognosis, restricting possible access to services - especially rehabilitation services - and excluding patients from the best medical, pharmacological and physiotherapeutic approach.

In our study, there was no significant difference between patients recovering and not recovering responsiveness in some of the variables potentially capable of influencing emergence (including late emergence) from VS. The duration of VS at the time of admission to the VSU, the cause of the brain injury, the time between the acute event and start of neurorehabilitation, and the CRS-R score on admission to the VSU were all found to have no effect. Patients suffering seizures were roughly twice as likely to progress to a minimally conscious state as those without seizures, although this was not statistically significant.

There is as yet no consensus on the interpretation of seizures in VS patients subsequently regaining consciousness. Electroencephalography does not seem to identify any specific patterns in VS or MCS, nor have any particular value in predicting the prognosis: in some cases, essentially normal tracings have been reported [6]. The alpha rhythm is associated with the emergence from VS, while there is a lack of systematic EEG data on MCS [44]. However, some investigators have described non-tonic-clonic SE in patients with altered consciousness [45-46], while Towne and colleagues stress that coma patients can present Nonconvulsive Status Epilepticus (NCSE), even without clear clinical epileptiform signs, and this may be an unrecognised cause of consciousness alterations [47]. Although on the basis of our caseload it is not possible to link anticonvulsant therapy with recovery of consciousness, EEG monitoring should be considered an essential part of the evaluation of VS and MCS patients to avoid both underdiagnosis and undertreatment, resulting in suboptimal management and outcome [48].

Conclusions

Statistical analysis confirmed that patients who recovered responsiveness were significantly younger than those who did not recover. Slow axonal regrowth in brain-damaged patients remains the most convincing hypothesis for biological mechanisms of late recovery [42]; it has been demonstrated in rats that axonal variations following brain injury are reversible [49].

Other elements, such as the application of a rehabilitative programme, may also favour recovery of consciousness, although literature data on the usefulness of such programmes are not particularly encouraging.

People with long-term consciousness disorders are often considered ineligible for admission to intensive rehabilitation facilities and once their medical problems have been stabilised in acute hospital treatment, many patients in a VS or MCS remain in long-term nursing facilities, with no specialised assessment or rehabilitative care.

As with Estraneo and colleagues [17], the intention of this study was not to establish the utility of rehabilitation with respect to recovery of consciousness. We are convinced that more intensive and earlyrehabilitation in patients with VS or MCS should be encouraged even if there is no clinical evidence to support this hypothesis. Failure to alert rehabilitation services, even after a substantial time has elapsed since the acute event, and the inability to recognise minimal or sporadic signs suggesting the emergence from a VS or MCS, could impede improvement in slow-to-recover patients with a brain injury.

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Table 1: NeurologicalStages of Recoveryfrom Brain Injury

Coma: eyes closed, no purposeful responses, no signs of wakefulness

Vegetative State (VS) - Unresponsive Wakefulness Syndrome (UWS): spontaneous eye opening, wakefulness, no cognitive awareness

Minimally Conscious State (MCS): inconsistent response to simple commands, simple but inconsistent purposeful behaviour

Emergence from MCS (EMCS): interactive communication and appropriate object use, severe attention deficits

Emerging Independence (EI): deficits in self-awareness and social awareness, developing functional independence in daily self-care, cognitive impairment in higher level attention, memory and executive functions

Table 2: Proportions of Patients Emerging from Vegetative State after Admission to vs Unit
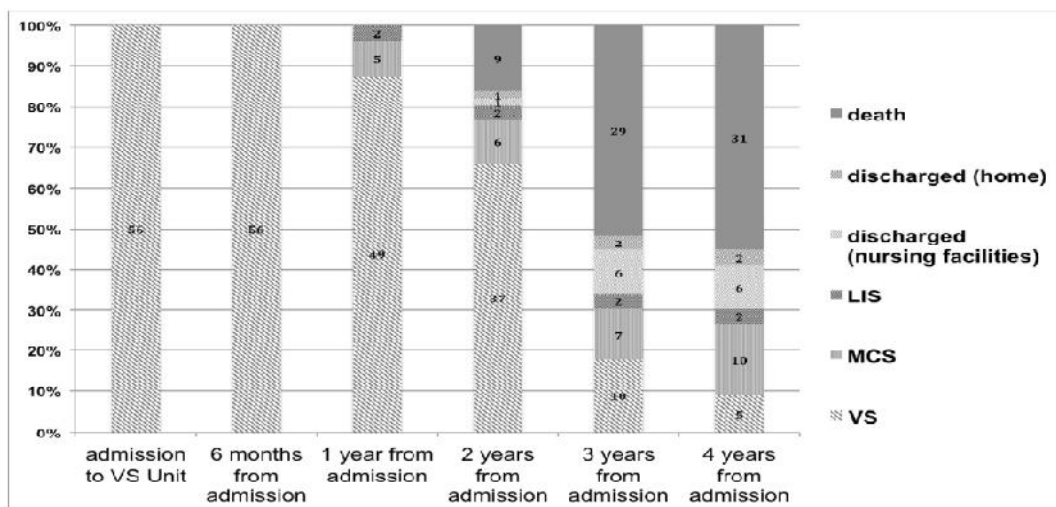
Table 3: Clinical and Demographic Features of 10 Sv Patients, 36 Months after Admission to vs Unit

PATIENT	SEX	AGE ON ADMISSION TO VS UNIT (years)	DURATION OF VS ON ADMISSION TO VS UNIT (months)	AETIOLOGY (A = anoxic, T = traumatic, H = haemorrhagic)	LENGTH OF HOSPITALISATION (from admission to VS Unit) (days)	CRS-R ON ADMISSION TO VS UNIT	CRS-R 48 MONTHS AFTER ADMISSION TO VS UNIT	NEUROIMAGING	LATE SEIZURES
1	F	31	6	A	156	2	2	Broad left temporoparietal lesion; ventricular enlargement*	NO
2	M	22	4	T	254	2	8	Diffuse cortical and subcortical atrophy	NO
3	F	9	3	T	178	2	2	Diffuse cortical and subcortical atrophy; ventricular enlargement*	NO
4	M	76	6	A	62	2	2	Broad bilateral temporoparietal lesion	YES
5	F	45	5	H	207	3	3	Broad left temporoparietal lesion; pontomesencephalic lesion	YES
6	M	58	2	T	336	2	2	Right frontal lesion: left parietal lesion	NO
7	M	37	3	T	379	3	11	Diffuse cortical atrophy; ventricular enlargement*	YES
8	F	78	3	H	66	2	6	Broad right temporooccipital lesion	NO
9	F	43	3	H	157	2	2	Diffuse cortical lesion; left parietal lesion	YES
10	F	51	2	H	93	2	2	Diffuse cortical and subcortical atrophy; bilateral lesions in thalamus	NO

Table 4: Descriptive Statistics of Variables Stratified on Diagnosis after 48 Months of Observation

		VEGETATIVE STATE (n=5)	MINIMALLY CONSCIOUS STATE (n=3)	DEAD (n=2)	Combined (n=10)	Statistical Test
Sex: M		20% (n=1)	67% (n=2)	20% (n=1)		Chi-square=1.81 d.f.=2 P=0.405
Age at coma onset		45.00/45.00/50.00*	28.50/37.00/57.50*	41.50/51.00/64.50*	31.75/45.00/56.00*	F=0.03 d.f.=2,7 P=0.973
Time from VS onset (months)		45.00/47.00/50.00*	35.00/45.00/50.00*	45.00/50.00/55.00*	40.25/50.00/55.00*	F=0.47 d.f.=2,7 P=0.645
Aetiology	Traumatic	20% (n=1)	33% (n=1)	0% (n=0)	20% (n=2)	Chi-square=4.33 d.f.=4 P=0.363
	Anoxic	20% (n=1)	33% (n=1)	100% (n=2)	40% (n=4)	
	Haemorrhagic	60% (n=3)	33% (n=1)	0% (n=0)	40% (n=4)	
CRS-R on admission ≤ 4		20% (n=1)	33% (n=1)	0% (n=0)	20% (n=2)	Chi-square=0.83 d.f.=2 P=0.659
CRS-R at 48th month		3.00/3.50/4.00*	6.00/8.00/11.00*	2.00/2.50/3.00*	2.00/2.00/5.50*	F=15.78 d.f.=2,7 P=0.003
Duration of coma (days)		25.00/25.00/25.00*	22.50/25.00/30.00*	33.75/47.50/61.25*	21.25/25.00/32.50*	F=0.07 d.f.=2,7 P=0.937
Widespread lesion		60% (n=3)	100% (n=3)	0% (n=0)	60% (n=6)	Chi-square=5 d.f.=2 P=0.082
Seizures: YES		20% (n=1)	100% (n=3)	50% (n=1)	50% (n=5)	Chi-square=0.14 d.f.=2 P=0.933

* For continuous variables, the figures represent respectively the median, the first and the third quartile of the distribution.