Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging

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Summary

Background The early post-traumatic vegetative state (VS) is compatible with recovery. Various clinical and laboratory tests have failed to predict recovery so we assessed the value of cerebral magnetic-resonance imaging (MRI) in prediction of recovery.

Methods 80 adult patients in post-traumatic VS had cerebral MRI between 6 weeks and 8 weeks after injury. MRIs were reviewed by three neuroradiologists for the number, sizes, and location of brain lesions. Three neurologists assessed the patients at the time of MRI and at 2 months, 3 months, 6 months, 9 months, and 12 months after injury using the Glasgow Outcome Scale.

Findings At 12 months, 38 patients had recovered while 42 patients remained in the VS. The demographic characteristics and causes and severity of injury were similar in patients in persistent VS (PVS) and those who recovered (NPVS). An average of 6·1 different brain areas were injured in patients in PVS compared with 4·6 areas in patients who had NPVS. Patients in PVS revealed a significantly higher frequency of corpus callosum, corona radiata, and dorsolateral brainstem injuries than did patients who recovered. Logistic regression analysis showed that corpus callosum and dorsolateral brainstem injuries were predictive of non-recovery. The adjusted odds ratios for non-recovery of patients with a corpus callosum lesion and dorsolateral brainstem injury were 213·8 (95% CI 14·2–3213·3), and 6·9 (1·1–42·9), respectively. In contrast, clinical characteristics, such as initial score on the Glasgow Coma Scale, age, and pupillary abnormalities failed to predict recovery.

Interpretation Cerebral MRI findings in the subacute stage after head injury can predict the outcome of the post-traumatic VS. Corpus callosum and dorsolateral brainstem lesions are highly significant in predicting non-recovery.

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Introduction

There is no more devastating or morally challenging condition in modern medicine than the persistent vegetative state (PVS).[1] The term vegetative state (VS) is used to describe the condition of patients with severe brain damage, in whom vegetative functions (sleep-wake cycles, autonomic control, and breathing) persist, but awareness (including all cognitive function and emotion) is abolished.[1–3] The estimated number of adult patients in PVS in the USA ranges from 10 000 to 25 000,[1] and in 1996 it was estimated that between US$1 billion and US$7 billion may be spent annually in providing their medical care.[4]

The diagnosis of a PVS can have a major influence on decision making concerning the level of care or services provided and may prompt an application to be made to the courts for a directive on withdrawal of tube feeding. Unfortunately, misdiagnosis of VS is not uncommon.[5] A report by Andrews and colleagues in 1996[6] provided evidence that up to 43% of patients were wrongly diagnosed as being in a VS. In addition, recovery from VS is not unlikely; half of the patients in post-traumatic VS may recover within 1 year of the injury.[7] Therefore, the first step in VS management requires correct clinical diagnosis. Moreover, ancillary diagnostic tests, in conjunction with a clinical assessment may provide important information for confirming a diagnosis of VS, and may also be helpful in predicting the potential recovery.

Various neurodiagnostic tests have been assessed in a quest for improved prediction of recovery from VS. These have largely centered on evoked potentials, the electroencephalogram, and cerebral computed tomography (CT). However, these tests have failed to predict the potential for recovery.

Magnetic resonance imaging (MRI) has been shown to be considerably more sensitive than cerebral CT for detection of traumatic and ischaemic cerebral lesions.[8,9] However, MRI has not been used to characterise the pattern of brain lesions in post-traumatic VS. Moreover, the value of cerebral MRI for prediction of recovery from a VS has not been investigated.

This study was done to define the MRI signs of cerebral injury in patients in post-traumatic VS. We also examined whether lesions in certain brain areas can predict that there will be non-recovery from a post-traumatic VS.

Patients and methods

The 80 patients who took part in the study were from a pool of adult patients with closed-head injuries, who were consecutively admitted to our trauma and rehabilitation centre between Jan 1, 1988, and March 31, 1996. Patients were enrolled in our study if VS continued to the subacute stage 6–8 weeks after injury. Patient's age, sex, initial pupillary response, initial score on the Glasgow Coma Scale (GCS), and time from injury to MRI were recorded.

Neurological outcome was scored on a consensus basis by at least three specialists in neurology according to the Glasgow Outcome Scale (GOS).[10] GOS score was obtained at the time of MRI, and at 2 months, 3 months, 6 months, 9 months, and 12 months after injury. Follow-up examinations were done up to 12 months after injury because recovery from VS more than a year

after the injury is considered highly unlikely.[7] VS was diagnosed according to the criteria described in the Multi-Society Task Force Report on PVS.[3] PVS was defined as a VS that has continued or endured for at least 12 months after injury. To allow comparison of patients in PVS and patients who recovered, the data of patients classified as severely disabled, moderately disabled, or as having made a good recovery were merged into a single category referred to as non-persistent vegetative state (NPVS).

The technical parameters for MRI included a field strength of 1·5 T and a slice thickness of 5 mm. Sagittal, axial, and coronal scans were obtained in all patients. Pulse sequences included a T2 weighted spin-echo sequence with a repetition time of 2000 ms and echoes of 20 ms and 90 ms, and a T1 weighted spin-echo sequence with repetition time of 600 ms and echoes of 15 ms. All patients were examined while being artificially ventilated under general anaesthesia. Written informed consent was obtained from the parents of all patients. The MRI films were assessed independently by three experienced neuroradiologists who were unaware of the medical histories of the patients. Differences in interpretation were resolved by consensus. The number, location, signal intensity, and size of each lesion was recorded. Sizes of lesions were scored as follows: 1+ as less than 1 cm in diameter; 2+ as 1 cm to 2·5 cm in diameter; and 3+ as more than 2·5 cm in diameter. Images were also examined for evidence of ventricular enlargement and cortical and brainstem atrophy.

Statistical analysis

The initial clinical characteristics and the frequency of MRI lesions (ie, one or more lesion at a certain location) in the PVS and NPVS groups were compared with the use of Fisher's exact test or the Mann-Whitney-U rank sum test, as appropriate. A logistic regression analysis was used to predict outcome based on clinical variables thought to have probable prognostic values in former studies[3] and MRI findings that revealed a significant difference in the univariate analysis. The final regression model included age, initial GCS score, pupillary abnormalities, total number of lesions, and the cerebral locations of the corpus callosum, dorsolateral upper brainstem, and corona radiata. Odds ratios and their 95% CIs were calculated to represent the relative risk of the explanatory variables.

Results

Most of the patients in PVS and NPVS groups were men, and the most common cause of head injury was a motor vehicle accident (table 1). The two groups did not differ significantly in terms of age, sex, pupillary abnormalities, or initial GCS score. The rates of incidence of a hypotensive episode in the prehospital setting (within 24 h of injury), and of a craniotomy for evacuation of an epidural or subdural haematoma were also similar in the PVS and NPVS patients. The frequency of medical complications, such as nosocomial infections, sepsis syndrome, and gastrointestinal bleeding was not significantly different in the two groups before or after the time of MRI. No sustained episodes of hypoxaemia (pO_2 <60 mm Hg for >5 min) or hypotension (systolic blood pressure <80 mm Hg for >5 min) were observed during the time the patients were in hospital.

42 patients remained in a VS 12 months after injury and 38 patients recovered within a year. Recovery had started in 24 (62%) of the patients by 3 months, and in 36 (94%) of the patients by 6 months after injury. Two (6%) of the patients showed signs of recovery from 6 months to 12 months after injury. Six (16%) of the patients had a good recovery, 13 (34%) a severe disability, and 19 (50%) a moderate disability. All patients who had a good recovery had shown signs of improvement within 6 months of injury. Among the 32 patients who recovered with a moderate or severe disability, 31 (98%) improved within 9 months of injury.

Characteristic	PVS at 12 months after injury (n=42)	NPVS at 12 months after injury (n=38)	p
Mean age (years; SD)	24·6 (7·5)	27 (8·2)	0·11
Mean injury to MRI interval (days; SD)	50 (4·4)	49 (4·2)	0·17
Sex			
Male	29 (69%)	27 (71%)	1
Female	13 (31%)	11 (29%)	
Initial GCS score			
3–5	29 (69%)	22 (58%)	0·36
6–8	13 (31%)	16 (42%)	
Pupillary abnormalities†	16 (38%)	13 (34%)	0·82
Cause of injury			
Motor vehicle accident	30 (71%)	26 (68%)	0·61
Skiing accident	4 (10%)	3 (8%)	
Cycling accident	3 (7%)	3 (8%)	
Fall	4 (10%)	2 (5%)	
Other	1 (2%)	4 (11%)	

PVS=persistent vegetative state; NPVS=non-persistent vegetative state; MRI=magnetic resonance imaging; GCS=Glasgow Coma Scale.
*Difference between the values in the PVS and NPVS groups.
†Pupillary abnormalities were defined as abnormalities in size or the reaction to light in one or both pupils.

Table 1: **Clinical and demographic characteristics**

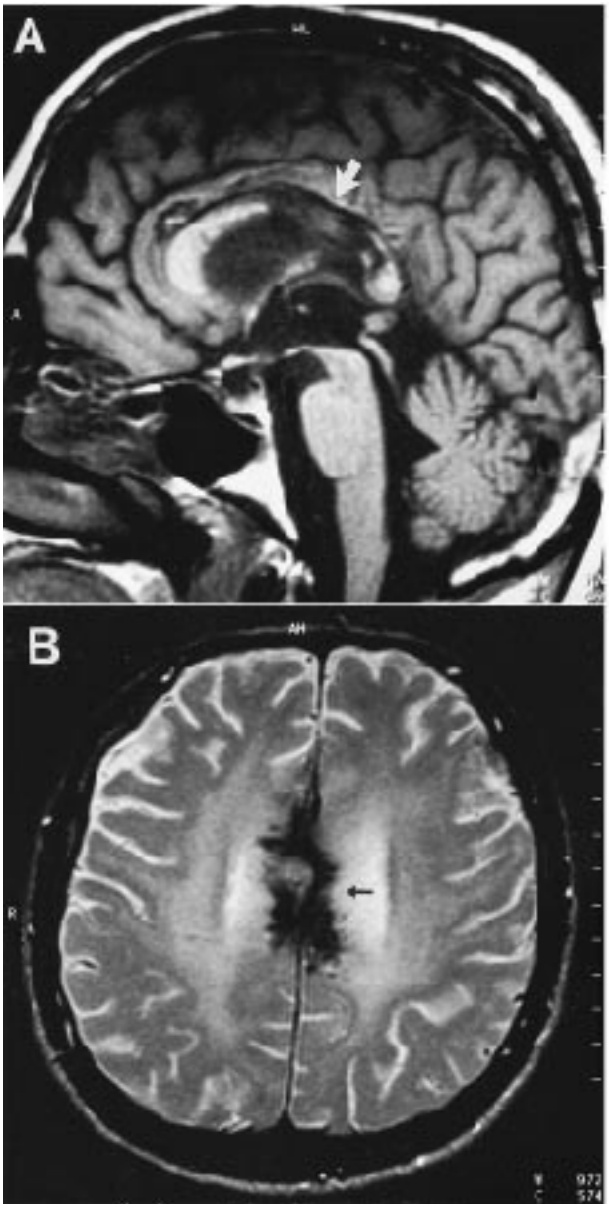
MRI findings

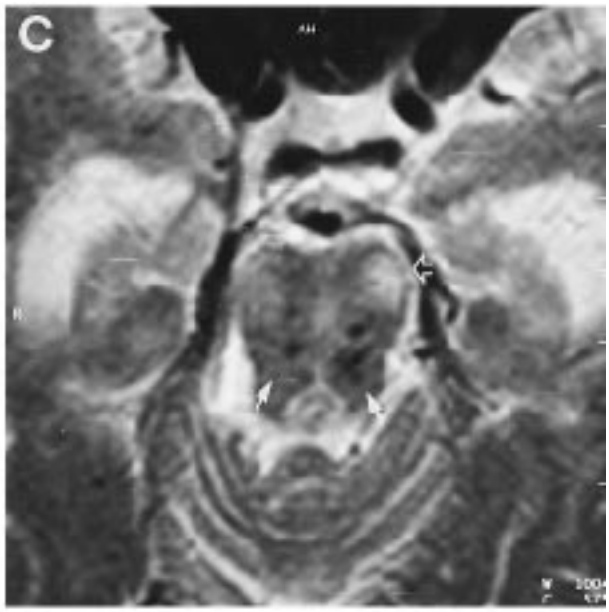
There was no significant difference in the mean time between injury and MRI between the PVS (50 days; range 42–56 days) and NPVS groups (49 days; range 43–55 days; table 1).

	PVS (n=42)*	NPVS (n=38)*	Odds ratio (95% CI)	p†
Supratentorial white-matter injury				
Corpus callosum	41 (98)	9 (24%)	132·1 (15·9–1100·6)	<0·001
Corona radiata	24 (57%)	10 (26%)	3·7 (1·5–9·6)	<0·01
Lobar white matter	22 (52%)	22 (58%)	0·8 (0·3–1·9)	0·66
Internal capsule	7 (17%)	5 (13%)	1·3 (0·4–4·6)	0·76
Cortical contusion				
Frontal lobe	11 (26%)	16 (42%)	0·5 (0·2–1·3)	0·16
Pole	7	9		
Superior region	4	6		
Orbitofrontal region	3	7		
Temporal lobe	10 (24%)	13 (34%)	0·6 (0·2–1·6)	0·33
Pole	4	5		
Lateral region	6	5		
Inferior region	2	3		
Parietal lobe	3 (7%)	2 (5%)	1·4 (0·2–8·8)	1
Occipital lobe	4 (10%)	3 (8%)	1·2 (0·3–5·9)	1
Subcortical grey-matter lesions				
Thalamus	17 (40%)	20 (53%)	0·6 (0·3–1·5)	0·37
Basal ganglia	22 (52%)	13 (34%)	2·1 (0·9–5·2)	0·12
Caudate nucleus	5	3		
Lentiform nucleus	19	12		
Hippocampal and parahippocampal lesions				
Hippocampus	9 (21%)	7 (18%)	1·2 (0·4–3·6)	0·79
Parahippocampal gyrus	19 (45%)	15 (39%)	1·3 (0·5–3·1)	0·66
Brainstem and cerebellar lesions				
Dorsolateral upper brainstem	31 (74%)	10 (26%)	7·9 (2·9–21·4)	<0·001
Ventral upper brainstem	21 (50%)	17 (45%)	1·2 (0·5–3·0)	0·66
Cerebral peduncles	18	15		
Ventral pons	10	8		
Medulla	5 (12%)	4 (11%)	1·1 (0·3–4·6)	1
Olive	5	4		
Cerebellum	9 (21%)	7 (18%)	1·2 (0·4–3·6)	0·79
Brain atrophy				
Ventricular enlargement	24 (57%)	14 (37%)	2·3 (0·9–5·6)	0·08
Cortical atrophy	11 (26%)	8 (21%)	1·3 (0·5–3·8)	0·61
Brainstem atrophy	12 (29%)	5 (13%)	2·6 (0·8–8·4)	0·11

MRI=magnetic resonance imaging. *Multiple combinations possible; percentages may not add to 100 because of rounding. †Difference between the values in the PVS and NPVS groups.

Table 2: **Frequency of MRI lesions by vegetative state 12 months after injury**





Sagittal T1 weighted (A) and axial T2 weighted (B,C) MRIs of a man aged 25 years examined 55 days after severe closed-head injury

All images show an extensive haemorrhagic lesion in the corpus callosum (white arrow, A; black arrow, B) and small focal haemorrhagic lesions in the dorsolateral brainstem (solid white arrows, C), consistent in appearance with diffuse axonal injury. In addition, a non-haemorrhagic lesion was detected within the left ventral pons (open white arrow, C) typical in location for a Wallerian degeneration of the left pyramidal tract. No signs of recovery from VS were observed within 1 year of injury.

Patients in PVS had a significantly higher frequency of supratentorial white-matter lesions of the corpus callosum and the corona radiata (ie, white matter adjacent to the central parts of the lateral ventricles above the level of the internal capsule) than did patients who recovered from the VS (table 2). Injury to the corpus callosum was detected in 41 (98%) of the patients in the PVS group compared with only nine (24%) of the patients in the NPVS group ($p<0·001$). The most common area of callosal injury in both groups involved the splenium and posterior body (figure A and B).

Injury to the corona radiata was found in 24 (57%) of the patients in PVS compared with ten (26%) of the patients in NPVS ($p<0·01$). Bilateral corona-radiata injury was more common than unilateral injury in patients in PVS and NPVS.

There was no significant difference in the frequency or local distribution of lobar white-matter injury between the two groups (table 2). 52% of the patients with PVS and 58% of the patients with NPVS revealed lesions in the lobar white matter. Lobar white-matter lesions were most common in the frontal and temporal regions, and less frequent in the parietal and occipital regions. The frequency of internal-capsule injury was similar in PVS (seven [17%]) and NPVS (five [13%]) patients.

The two groups did not differ in the frequency or local distribution of cortical contusions (table 2), which were found in 20 (48%) of the patients in PVS and in 19 (50%) of the patients in NPVS. The frontal lobe and the temporal lobe were the most common regions of cortical injury in both groups. Most frontal and temporal contusions involved the frontal pole and the lateral aspects of the temporal lobe, respectively.

The frequency of thalamic and ganglionic lesions was similar in both groups (table 2). 17 (40%) of the patients in PVS and 20 (53%) of the patients in NPVS had thalamic lesions. In addition, 22 (52%) of the patients in PVS and 13 (34%) of the patients in NPVS had lesions within the basal ganglia. In both groups injury of the lentiform nucleus was more common than of the caudate nucleus.

Hippocampal injury was detected in nine (21%) of the patients in PVS and in seven (18%) of the patients in NPVS (table 2). In addition, the frequency of parahippocampal injury was similar in patients in PVS (19 [45%]) and patients in NPVS (15 [39%]).

Supratentorial lesions ranged in size from 1+ to 3+. In general, white-matter and subcortical grey-matter lesions were smaller than cortical contusions. However, a statistical analysis of the mean lesion sizes for each location revealed no significant difference between the two groups.

Patients in PVS had more injuries to the dorsolateral upper brainstem than did patients who recovered from the VS (31 [74%] *vs* ten [26%]), respectively; $p<0·001$; table 2; figure C). Injuries to the brainstem tegmentum were more common than were periaqueductal or tectal lesions.

The frequency of lesions of the upper ventral brainstem

Logistic regression analysis	Adjusted odds ratio (95% CI)	p
Age	1 (0·9–1·1)	0·84
GCS score (3–5 *vs* 6·8)	1·8 (0·3–9·9)	0·49
Pupillary abnormalities (yes *vs* no)*	0·5 (0·1–2·6)	0·4
Corpus callosum	213·8 (14·2–3213·3)	<0·001
Dorsolateral upper brainstem	6·9 (1·1–42·9)	<0·05
Corona radiata	1·1 (0·1–8·2)	0·96
Total number of cerebral lesions	1·2 (0·9–1·6)	0·3

GCS=Glasgow Coma Scale. *Pupillary abnormalities were defined as abnormalities in size or the reaction to light in one or both pupils.

Table 3: **Predictors of non-recovery**

and the medulla oblongata was similar in the two groups (21 [50%] and five [12%] for PVS and 17 [45%] and four [11%] for NPVS, respectively; table 2). Injury to the medulla oblongata was exclusively localised in the olivar area. In addition, similar frequencies of cerebellar lesions were seen in the PVS (nine [21%]) and in the NPVS (seven [18%]) group. The sizes of infratentorial lesions ranged from 1+ to 2+ and did not significantly differ between the two groups.

There was no statistical difference in the frequency of supratentorial ventricular enlargement, cortical atrophy, or brainstem atrophy between the two groups (table 2).

Multiplicity of lesions

Patients in PVS had more cerebral lesions (mean 10·4; range 5–19), than did patients who recovered from a vegetative state (mean 7·9; range 3–18, p<0·001). Only the number of corpus callosum, corona radiata, and dorsolateral upper brainstem lesions was significantly higher in the PVS group when compared with the group of patients in NPVS (p<0·001 for each location).

Four to ten (mean 6·1) and three to seven (mean 4·6; p<0·001) different cerebral locations were injured in patients in the PVS and NPVS groups, respectively. The most common combination of injuries in the PVS group (30 [71%]) was callosal and dorsolateral brainstem injury. In patients in NPVS the combination of lobar white-matter injury and ventral-brainstem injury was detected most often (11 [29%]).

Prognostic factors

A logistic regression was done to assess the usefulness of patient characteristics and imaging features in predicting outcome from a VS (ie, NPVS *vs* PVS). The variables age, GCS score, and pupillary reactivity were included in the model together with variables corpus callosum, dorsolateral upper brainstem, corona radiata, and total number of cerebral lesions, which were significant at univariate analysis. Because the number of lesions and number of locations are highly correlated (0·73), the number of lesions was not included in the model. The analysis of results is shown in table 3. In contrast, there was an association between MRI findings and non-recovery from VS: patients in a VS with lesions in the corpus callosum or dorsolateral brainstem had a 214-fold and seven-fold higher probability for not recovering, respectively (adjusted odds ratios for age, GCS score, pupillary abnormalities, and total number of lesions). The final model showed a correct classification rate of 87·5% between observed and predicted group membership.

Discussion

Our data suggest that cerebral MRI may assist in early prediction of outcome from a post-traumatic VS. Our findings indicate that lesions of the corpus callosum and the dorsolateral upper brainstem are predictive of a patient not recovering. Clinical features such as initial GCS score, pupillary reactivity, and patient age failed to predict recovery from a VS.

Because of the prognostic and therapeutic uncertainties concerning VS, several professional medical organisations began a comprehensive examination of their standards of medical care for patients with this condition.[1,3,7,11] Moreover, several studies have focused on the value of clinical and neurodiagnostic tests to predict the potential for recovery from a VS. For example, some evidence suggests a correlation between PVS and advanced age, the presence of pupillary abnormalities, and a low score on a test of motor responses.[12] In contrast, a report by Levin and colleagues[13] provided evidence that these parameters cannot predict recovery. Our results confirm that patient age, low GCS score, and pupillary abnormalities are unreliable in this regard.

Neurodiagnostic tests have largely centered on neurophysiological measures such as evoked potentials and the electroencephalogram. However, results in patients in a post-traumatic VS vary widely, and are probably of little value in predicting outcome.[3,14–17] Cerebral metabolic and cerebral-blood-flow measurements after acute neurological injury, likewise do not predict outcome. Although positron emission tomography has shown a reduction in the cerebral metabolism of glucose in patients in a PVS, there is not yet sufficient information to warrant the use of such scanning to determine prognosis.[3] There is also some evidence that cerebral blood flow is reduced in patients in a post-traumatic PVS.[18] In contrast, other studies have found normal cerebral-blood-flow patterns in patients in a PVS.[19] Lastly, a recent report indicated that cerebral computed tomography does not predict future recovery from post-traumatic VS.[15] Importantly however, it is apparent from studies of pathology that computed tomography underestimates the severity of many forms of cerebral injury, such as corpus callosum and brainstem injury.[20,21] Although callosal and brainstem injury is a major neuropathological feature in post-traumatic VS,[22] patients in the latter computed-tomography study had no evidence of lesions in these regions.[13] Therefore, cerebral computed tomography seems unreliable for classifying and staging the severity of cranial trauma. Cerebral MRI however, has been found to be far superior to computed tomography in the detection of traumatic cerebral lesions.[21–24] There is much evidence suggesting that cerebral MRI may now permit accurate identification and classification of all types of traumatic lesions, in particular in the subacute stage after head injury.[8]

Neuropathological data indicate that diffuse axonal injury may be the most common pathological feature of brain injury in patients dying in a post-traumatic PVS.[22,25,26] In its most severe form, diffuse axonal injury is reflected by two macroscopic features: lesions in the corpus callosum and in the dorsolateral upper brainstem.[27,28] Comparison of the anatomical distribution of lesions in our patients with that in pathological studies suggests that diffuse axonal injury is also a major form of primary damage to the brain of patients surviving in the PVS. Moreover, our findings suggest that lesions of the corpus callosum and of the dorsolateral upper brainstem may predict that there will be no recovery from a VS. In contrast, 24% of patients with a corpus-callosum lesion and 26% of patients with dorsolateral-brainstem injury were not vegetative 1 year after the injury. However, no patient in the NPVS group with a corpus-callosum or dorsolateral-brainstem injury made a good recovery. Therefore, our data indicate that

lesions within these regions may correlate with unfavourable outcome after traumatic brain injury. However, future studies are required to investigate the specific contribution of corpus callosum and dorsolateral brainstem injury, or both, for the prediction of non-recovery from a post-traumatic VS.

The frequency of corpus-callosum lesions (63%) and of dorsolateral-brainstem lesions in this study (52%) is higher than in other MRI series where the frequency of callosal and dorsolateral brainstem injury did not exceed 47% and 28%, respectively.[20,21] Several factors might explain this disparity. First, our study population was homogeneous as regards type and chronicity of injury. Moreover, we found a higher severity of injury than in other MRI series as reflected by lower initial GCS score that may have also contributed to the higher frequency of callosal and dorsolateral brainstem lesions found in our study. Also, a higher degree of injury is more likely to be associated with lesions in these regions.

Our data agree with neuropathological findings that indicate that cerebral lesions in the post-traumatic VS are not restricted to a single locus.[22] In fact, the multiplicity of lesions at various locations may help explain the many manifestations of sensory, pyramidal, extrapyramidal, and cerebellar abnormalities seen clinically in VS. Our data indicate, however, that additional injury to the corpus callosum and the dorsolateral upper brainstem may be of importance for the persistence of a post-traumatic VS. Some reports also suggest that callosal or dorsolateral brainstem injury contributes to deficits in attention and awareness.[29,30] Therefore, one could speculate that the long-term lack of these functions, as seen in the PVS, may be due to a combination of callosal, dorsolateral brainstem, and cerebral lesions in different regions. A report by Kinney and Samuels[22] suggested that a combination of cerebral lesions may in some way exert a cumulative effect and underlie the PVS. Future studies must investigate whether specific combinations of cerebral lesions contribute to PVS.

The value of our study is limited by the lack of follow-up MRI examinations in all our patients. For example, it seems possible that severe complicating medical factors, in particular sustained episodes of hypoxaemia or hypotension may have affected the pattern of brain lesions detected in the subacute phase after trauma. However, no severe hypotensive or hypoxaemic episodes were recorded after the MRI examinations in patients in PVS or in NPVS, which makes it unlikely that additional hypoxic-ischaemic brain damage occurred. The nature and severity of neuroradiological changes detected in the early stages after trauma may indeed reflect the anatomical basis for a PVS and NPVS, respectively.

We provide evidence that cerebral MRI in the subacute stage after trauma may predict the potential for recovery from a post-traumatic VS. However, future rigorous clinical, neuroradiological, and pathological correlative studies will be needed if we are to acquire a better understanding of the factors contributing to recovery from a VS.

Contributors

Andreas Kampfl, Erich Schmutzhard, Gerhard Franz, Bettina Pfausler, and Hans-Peter Haring were responsible for the clinical care and recruitment of the patients. Stefan Felber, Stefan Golaszewski, and Franz Aichner were responsible for the interpretation of the MRI scans. Gerhard Franz was responsible for entering the data into a computerised database. Hanno Ulmer did the statistical analysis. The paper was written by Andreas Kampfl with contributions from all other investigators.

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References

1 Zeman A. Persistent vegetative state. *Lancet* 1997; **350:** 795–99.
2 Jennet B, Plum F. Persistent vegetative state after brain damage. *Lancet* 1972; i: 734–37.
3 The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (first of two parts). *N Engl J Med* 1994; **330:** 1499–508.
4 Payne K, Taylor RM, Stocking C, Sachs GA. Physicians' attitudes about the care of patients in the persistent vegetative state: a national survey. *Ann Intern Med* 1996; **125:** 104–10.
5 Childs NL, Mercer WN, Childs H. Accuracy of diagnosis of persistent vegetative state. *Neurology* 1993; **43:** 1465–67.
6 Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. *BMJ* 1996; **313:** 13–16.
7 The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (second of two parts). *N Engl J Med* 1994; **330:** 1572–79.
8 Gentry LR. Imaging of closed head injury. *Radiology* 1994; **191:** 1–17.
9 Ramadan NM, Deveshwar R, Levine SR. Magnetic resonance and clinical cerebrovascular disease. An update. *Stroke* 1989; **20:** 1279–83.
10 Jennet B, Bond M. Assessment of outcome after severe brain damage: a practical scale. *Lancet* 1975; i: 480–84.
11 The permanent vegetative state. *J R Coll Physicians Lond* 1996; **30:** 19–21.
12 Braakman R, Jennet WB, Minderhoud JM. Prognosis of the posttraumatic vegetative state. *Acta Neurochir* 1988; **95:** 49–52.
13 Levin HS, Sajdjari C, Eisenberg HM, et al. Vegetative state after head injury. A traumatic coma data bank report. *Arch Neurol* 1991; **48:** 580–85.
14 Ahmed I. Use of somatosensory evoked responses in the prediction of outcome from coma. *Clin Electroencephalogr* 1988; **19:** 78–86.
15 Judson JA, Cant BR, Shaw NA. Early prediction of outcome from cerebral trauma by somatosensory evoked potentials. *Crit Care Med* 1990; **18:** 363–68.
16 Lindsay K, Pasaoglu A, Hirst D, Allardyce G, Kennedy I, Teasdale G. Somatosensory and auditory brain stem conduction after head injury: a comparison with clinical features in prediction of outcome. *Neurosurgery* 1990; **26:** 278–85.
17 Hansotia PL. Persistent vegetative state: review and report of electrodiagnostic studies in eight cases. *Arch Neurol* 1985; **42:** 1048–52.
18 Oder W, Goldenberg G, Podreka I, Deecke L. HMPAO-SPECT in persistent vegetative state after head injury: prognostic indicator of the likelihood of recovery? *Intensive Care Med* 1991; **17:** 49–53.
19 Agardh CD, Rosen I, Ryding E. Persistent vegetative state with high cerebral blood flow following profound hypoglycemia. *Ann Neurol* 1983; **14:** 482–86.
20 Gentry LR, Thompson B, Godersky JC. Trauma to the corpus callosum: MR features. *AJNR* 1988; **9:** 1129–38.
21 Gentry LR, Godersky JC, Thompson BH. Traumatic brain stem injury: MR imaging. *Radiology* 1989; **171:** 177–87.
22 Kinney HC, Samuels MA. Neuropathology of the persistent vegetative state. A review. *J Neuropathol Exp Neurol* 1994; **53:** 548–58.
23 Gentry LR, Godersky JC, Thompson B. MR imaging of head trauma: review of the distribution and radiopathological features of traumatic lesions. *AJNR* 1988; **9:** 101–10.
24 Orrison WW, Gentry LR, Stimac GK, Tarrel RM, Espinosa MC, Cobb LC. Blinded comparison of cranial CT and MR in closed head injury evaluation. *AJNR* 1994; **15:** 351–56.
25 Peters G, Rothemund E. Neuropathology of the traumatic apallic syndrome. In Dalle Ore G, Gerstenbrand F, Luecking CH, Peters G, Peters EH, eds. The apallic syndrome. New York: Springer Verlag, 1977: 78–87.
26 Jellinger K. Pathology and pathogenesis of apallic syndromes following closed head injuries. In: Dalle Ore G, Gerstenbrand F, Luecking CH, Peters G, Peters EH, eds. The apallic syndrome. New York: Springer Verlag, 1977: 89–103.
27 Adams JH, Graham DI, Murray LS, Scott G. Diffuse axonal injury due to non-missile head injury in humans: an analysis of 45 cases. *Ann Neurol* 1982; **12:** 557–63.
28 Graham DI, Gennarelli TA. Trauma. In: Graham DI, Lantos PL, eds. Greenfields neuropathology, 6th edn. New York: Arnold, 1997: 197–62.
29 Wuillemuier P, Assal G. Lesions of the corpus callosum and syndromes of interhemispheric disconnection of traumatic origin. *Neurochirurgie* 1995; **41:** 98–107.
30 French JD. Brain lesions associated with prolonged unconsciousness. *Arch Neurol Psychiatry* 1952; **68:** 727–40.