

REVIEW ARTICLE

The Vegetative State: A Review of Etiology and Prognostic Factors

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ABSTRACT This paper reviews the research investigating the vegetative state (VS) in terms of its aetiology and prognostic factors that may be indicative of the outcome for patients in the VS. The VS is a relatively rare syndrome that still causes confusion for treating clinicians. In short, the VS is a clinical condition of unawareness of self and environment but with retained wakefulness. Until relatively recently there were no universally accepted diagnostic criteria, which caused problems both in terms of diagnosing the patient and in determining the incidence of the VS. This paper examines the most relevant and up to date work in order to determine if there is a way of predicting whether the VS for any given patient will be persistent (i.e. recovery is still possible) or if it is permanent and further treatment is futile. Currently, the most accurately available method to predict the prognosis of a patient in the VS is through clinical assessment of the patient combined with knowledge of the aetiology and duration of the VS. More work is needed in order to allow for the prediction of the outcome of the VS with greater certainty.

INTRODUCTION

While the advent of cardiopulmonary resuscitation during the 1960s was a breakthrough for medical science, some survivors remained in a limbo state of 'waking unconsciousness'. It was Jennett and Plum (1), in 1972, who termed this condition the persistent vegetative state (PVS) and described the vegetative state (VS) as:

> The absence of any adaptive response to the external environment, the absence of any evidence of a functioning mind which is either receiving or projecting information in a patient who has long periods of wakefulness

In short, the VS is a clinical condition of unawareness of self and environment but with retained wakefulness. Efforts to predict the outcome of patients in a vegetative state began around this time due to the concern that large numbers of patients surviving in a VS would be costly and use resources that could be more effectively spent elsewhere (2).

The incidence of the VS is unknown, partly because of the rarity of the condition and partly because of the lack of accepted universal diagnostic criteria. Estimates range from 0.4-1.1/100,000 people throughout the world (3,4). Moreover, until 10 years ago, the VS was not a codable diagnosis in either the International Classification of Diseases or most health agencies. Studies at the time suggested that the prevalence in the United States alone was around 10,000-25,000 adults and 4000-10,000 children (3,4).

The VS causes distress to family and friends and creates difficulties for the doctors involved. To the non-medically trained, a patient in the VS may appear to be alive and functioning; for example they may seem to smile or turn to sound despite the fact that by definition the patient is not aware. This may cause conflict between the family of the patient and the doctors who are trying to explain what the VS is and the likely outcome. This may be further complicated by the fact

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that prediction of recovery is an inexact science. Doctors cannot give a definite answer and the family may prefer to simply watch and wait while they feel there is still hope. To provide the care that the patient needs, the doctor must have the ability to predict the best possible outcome and also to recognize when it would be more humane to withdraw medical interventions and let nature take its course. The ethical dilemmas regarding quality of life and best intentions are many and complex, and as such, are beyond the scope of this review. This paper reviews the research investigating the vegetative state (VS), in terms of its etiology and prognostic factors that may be indicative of the outcome for patients in the VS. Furthermore, this review identifies the methods by which prediction of prognosis may be possible.

METHODS

A literature search was conducted in Medline (from 1993) and EMBASE (from 1980) to identify suitable papers. The databases limited the choice of date selection; the selected dates were chosen to identify only the most up to date work. The keywords used were PVS, VS, (persistent) vegetative state, (permanent) vegetative state, children and (persistent, permanent) vegetative state, coma or life support care, combined with prognosis or prediction. The aim in the use of the keywords was to detect all relevant articles in the given time period. In all, about one hundred articles were identified but not all of the papers were applicable to the aims of this review. The reference lists of relevant articles were scrutinised to detect any additional studies that had not been already identified. The articles most applicable to the subject were selected and the information within them collated, with careful attention being paid to the methods of the systematic reviews and critical analysis of the original studies that warranted inclusion.

CONSCIOUSNESS AND THE VEGETATIVE STATE

There are two components to consciousness (3):

1. Wakefulness

Clinical work indicates that the midline structures in the upper pons, midbrain and thalamus (the reticular activating system or RAS) are necessary for wakefulness. They are activated by arousal and influence the cerebral cortex directly. Wakefulness is essentially not being asleep; therefore it comprises acts that one would not do while asleep such as opening one's eyes and looking around.

2. Awareness

The cerebral cortex and its projections to the major subcortical nuclei are considered to be the root of awareness with its content being the mass of information that it processes from the external environment. Awareness comprises behaviours that indicate that a person comprehends the outside environment (e.g.: communication and understanding).

As one of the main links between the two component areas, the thalamus is crucial to the preservation of consciousness (3,5). Unconsciousness therefore implies global (or total) unawareness. Awareness requires wakefulness, but wakefulness can be present without awareness. In the comatose state both awareness and wakefulness are lacking, while in the VS wakefulness is preserved and awareness is not (3).

If the VS lasts for a month, it is termed continuing or persistent VS (3,6). The consensus is that the terminology changes to that of permanent VS when the condition is deemed to be irreversible, no recovery seems possible and further treatment is considered futile. This decision is usually taken once a year has elapsed in traumatic aetiologies and after three months in non-traumatic cases (4-6). However, as with all clinical judgements, it is based on probabilities. While persistent VS is a diagnosis, permanent VS is a prognosis. In practise, the terms are commonly used interchangeably and the acronym PVS is used for both conditions (3,5-7). Therefore, the acronym VS will be used in this review, and distinguished where necessary if specific reference is being made to a persistent or permanent state. Recovery from the VS is classified by the Glasgow Outcome Scale (GOS, see Table 1), with a good recovery indicated by a GOS score of 4 or 5.

Table 1. The Glasgow Outcome Scale (GOS). (4).

Level	Term	Definition
1	Dead	No life
2	Vegetative state	Unaware of self and envirion
3	Severe disability	Uable to live independently
4	Moderate disability	Able to live independently
5	Mild disability	Able to return to work/school

Diagnosing the VS

Before a diagnosis of the VS can be made, an established cause must be found and all reversible factors that may be contributing (e.g. metabolic disturbances, sedatives, anaesthetics or neuromuscular blocking drugs) eliminated (5).

The Multi-Society Task Force (MSTF) on persistent VS defined the following diagnostic criteria, which are widely acknowledged by the medical community (3):

1. No evidence of awareness of self or environment and an inability to interact with others.
2. No evidence of sustained, reproducible, purposeful or voluntary behavioural responses to visual, auditory,

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

Patients in the VS are usually not immobile. There may be apparent semi-coordinated movements such as scratching, moving hands towards noxious stimuli (such as during mouth care) and reflex grasping. There is flexor withdrawal after a delay; inflicting a painful stimulus such as pressing the supraorbital ridge causes a stereotyped flexing of limbs as during assessment of Glasgow Coma Scale status (GCS, see Table 2). Movements are slow, dystonic and obviously abnormal. Neck movements may provoke reflex postural alterations. There may be chewing and grinding of teeth, and food and liquid placed into mouth may be swallowed. Patients in the VS may retain the response of turning their head or moving their eyes to sound, but eye fixation and tracking is not demonstrated. They may smile or appear to shed tears, and may grunt or groan (vocalise) but never speak (verbalise) (3,5-7). Although this may be disturbing to family and carers, it should be remembered that by definition patients in the VS have no awareness, and therefore it is the opinion of experts on the subject that they cannot feel any pain (4-7).

Table 2. The Glasgow Coma Scale (GCS).

Eye Opening (eGCS)	Motor Response (mGCS)	Verbal Response (vGCS)
1. No response	1. No response	1. No response
2. Open to pain	2. Abnormal Extension	2. Incomprehensible
3. Open to verbal command	3. Abnormal Extension	3. Inappropriate
4. Open spontaneously	4. Withdrawal	4. Confused
	5. Localises to pain	5. Fully orientated
	6. Obeys commands	

Diagnostic problems

Determining cognitive awareness in another person can only ever be an educated guess as there are no tests that can confirm the presence or absence of inner awareness (3,6-8). Repeated assessment is therefore essential, especially if there is some doubt over whether the behavioural patterns necessary for diagnosis of the VS are present.

The diagnosis of the VS is difficult to make in infants younger than three months because they have a limited capacity to show higher cognitive functions; the differentiation between voluntary and involuntary responses may also be unreliable until this age. The concept of the VS cannot be applied to preterm infants because of developmental immaturity and the lack of consistently recognisable sleep-wake cycles. The exception is infants born with severe developmental malformations such as anencephaly and hydranencephaly where there is minimal or no cerebral cortex and therefore no awareness. These infants are categorised as being in a VS congenitally (3,8).

PATHOPHYSIOLOGY AND ETIOLOGY OF THE VS

The VS is largely characterised by a functioning brainstem with no input from the cerebral hemispheres due to either disconnection or damage of two main types (3):

1. *Acute*, e.g. head injury, hypoxic-ischaemic damage following cardiopulmonary arrest, metabolic disturbances.
2. *Chronic*, e.g. degenerative processes such as Alzheimer's disease, congenital defects such as anencephaly.

The VS can be caused by a vast array of conditions; with any insult to the body that causes damage to the cerebral cortex being a potential cause of the VS. Three main patterns of brain pathology are seen at autopsy (3,9):

1.*Diffuse Axonal Injury* (DAI), which is extensive subcortical axonal injury that virtually isolates the cortex from other parts of the brain. It is most commonly due to the shearing forces in trauma or sometimes to hypoxic-ischaemic insults and is the most common pathological feature seen.
2.*Extensive laminar necrosis* is due to acute global cerebral ischaemia or hypoxia. Multifocal or diffuse necrosis is seen with almost invariable involvement of the hippocampus, hypothalamus and brainstem.
3.*Relatively selective thalamic necrosis* is an uncommon observation that may follow acute global ischaemia. Specific anatomical boundaries are not well described.

Mixtures of all three lesions are commonly seen with additional focal lesions depending on the precipitant of the insult. Acutely inflicted hypoxic-ischaemic insults and shearing forces are therefore shown to have a devastating impact on the brain, as these are the most frequently seen pathologies at autopsy. There have also

been reports of rare isolated lesions of the brainstem or hypothalamus alone causing the VS but these are not well studied (3).

The diagnosis of permanent VS is made by identification of cause, fulfilling diagnostic criteria and lasting for at least a set amount of time (three months for non-traumatic aetiologies, one year for traumatic) (6). Therefore, there are two aspects to the prediction of whether the VS will be permanent or whether recovery is possible - the etiology of brain insult and the duration of the VS to date.

1. Etiology of Brain Insult

Outcome of coma is directly related to its cause (2), which can be separated into two aetiologies: traumatic (e.g. road traffic accidents, falls) and non-traumatic (e.g. cardiac or pulmonary arrest, anoxic- ischaemic, metabolic).

Traumatic

Traumatic etiology of brain injury is the better of the two categories. The MSTF collated data from several similar studies of traumatic brain injury giving information on outcome for 434 patients (4). Recovery of consciousness varied with time, with 88% of those who recovered (46% of all patients studied) doing so within the first six months, and reaching 99.98% at one year. After this, recovery was rare. Only seven of the 434 (0.02%) recovered after this time, between one and three years after the injury. Five of them remained severely disabled, one was moderately disabled and the status of the seventh was undeterminable. Five of the seven were under 30 years, suggesting that age is another important confounding factor in the prediction of prognosis. Accordingly, those under 40 had a greater chance of recovering within three months without severe disability (4). Children in traumatic coma generally have a better prognosis than adults in a similar condition, although recovery of function is comparable (4,10). Data from several similar studies showed that 62% of children had regained consciousness at one year following injury, compared to 52% of adults (4,8).

Traumatic brain injury is also associated with a poor chance of a good functional recovery as described by the GOS (see Table 1). Using the collated data (4), from the 434 patients in a VS, of the 52% who had recovered consciousness by one year, 28% had severe disability, 17% moderate disability and only 7% had made a good recovery. Of those who made a good recovery over half showed signs of improvement within the first three months and all within six months. Those who recovered consciousness but remained disabled all began to show signs of improvement three to six months after the brain injury. This indicates that a later recovery was almost always associated with severe disability (4).

Non-traumatic

Non-traumatic etiology carries a much poorer prognosis than its traumatic counterpart. Collecting data on the outcome of 169 patients in a systematic analysis (4) showed 85% or more died within the first month or remained in a VS. Of the remaining 15% who recovered consciousness (11% of which were within the first three months, and the other 4% by six months), only one patient (0.6%) made a good recovery. One year after the injury, 32% remained in persistent VS and 53% had died. A larger study of 500 patients by Levy et al. (11) found that at one year, 73% were dead or in a VS and of the remaining 27%, 11% were severely disabled, 4% were moderately disabled and 12% (2.4% of the total) had made a good recovery. They agreed that most improvement occurred within the first month and that the longer the VS persisted, the smaller the chance of recovery.

There is very little evidence to suggest that there is a consistent relationship between age and prognosis in non-traumatic coma, mainly due to a lack of data (4,11). Shewmon (10) suggests that in children (under 16 years), the outcome is either full neurological recovery or remaining in a VS with very few outcomes in-between, with ratios ranging from 50:50 to 70:30 in favour of intact functioning. The commonest cause of non-traumatic coma in children is near drowning, and Shewmon (10) postulates that childrens' brains are more protected against anoxic-ischaemic damage due to their body temperature falling faster because of their smaller size. No evidence was found to confirm this, but it appears that children are less susceptible to anoxic or ischaemic injury and have a greater potential for neurological recovery than adults. As a result of this, the observation period in children is often allowed to be longer than the standard three months that adults are given before their VS is declared permanent (8).

Specific etiology

The underlying cause of the coma has been shown to relate to outcome in many studies (2,4,11). Metabolic and diffuse disorders carried a better prognosis than hypoxic-ischaemic causes (2,4,11). Cerebrovascular disease such as subarachnoid haemorrhage or stroke and other disorders causing structural brain damage carried the worst prognosis of all (2,4,11). The incidence of a VS was also observed to be higher following anoxic-ischaemic injury; for 20% of the patients studied this was the best outcome that they ever achieved (GOS 2) (2,11). Drug overdose also carried a favourable prognosis due to the reversibility of their effects, despite a bleak outlook at initial assessment that was considered to be due to depressive effects on the brainstem (2).

2. Depth and Duration of Coma

The longer the patient remains in a coma, the poorer their chance of recovery and the greater the chance that they will enter a VS (2,11). A week is often used as a cut-off point; by that time the chance of a moderate or good recovery is only 6-7% and almost half of those who are still unconscious will be in a VS (2,11). By convention, one month after the brain injury the patient is in a persistent VS (6) and the chance of recovery is small. However, studies by Andrews (12) and Dubroja and colleagues (13) have shown that recovery is possible beyond this time. In one case, recovery began three years after the initial insult (13). Whilst this shows that higher functioning can be regained beyond predictions, it should be noted that these studies only looked at small groups and that no one in them made a complete recovery. There have been other documented cases of very late recovery (4) but in all of them the level of function was far from independent. Such outcomes may be undesirable to some, but to others this may be an acceptable quality of life.

PROBLEMS WITH PROGNOSIS ACCURACY

Predicting prognosis in the VS is an inexact science and there are faults that are common to all the studies considered. The rarity of the condition itself (often resulting in studies with small sample sizes) coupled with the inability to conduct true prospective studies has led to many of the published papers lacking sufficient power to demonstrate their value. There are inevitable confounding factors in the studies, such as patients dying of non-neurological disease during the studies and the fact that in many studies no distinction is made between the VS and death, or the VS is combined with severe disability as a non-acceptable outcome. The studies are also limited by ethical considerations, as ideally patients would be kept alive indefinitely. Doctors are bound to act in their patient's best interests if the patient cannot express their own views. It can be argued, that keeping a patient in the VS simply for means of a scientific study is not in the patient's best interests and therefore is unethical. Short follow-up times are also commonplace. In addition, the studies face the problem of self-fulfilling prophecies [i.e. if a patient is predicted to have a poor outcome, it has been shown that therapies are often less aggressive and the next of kin are more likely to ask for withdrawal of medical support (2)].

Improvement on previous studies is difficult. Despite recognised problems with their methodology, it is not easy to correct them. We cannot alter the small sample sizes or the lack of prospective studies because of the rarity of the condition itself and because the ethical problems remain the same. This will most likely continue to be a problem unless a large scale, multicentre trial is organised with the cooperation of a large number of major neurological centres around the world.

Age

As has already been implied, the age of the patient may hold prognostic significance. Shewmon (10) states that children (under 16 years) have a better chance of recovering consciousness, although their functional recovery is often equivalent to that of adults. He asserts that the mortality rate from severe head injury declines with increasing age in childhood, reaching a trough at 14-15 years and then rising with age throughout adulthood. However, others have shown that outcomes worsen with rising age, even in childhood, which is possibly related to age specific differences in types of trauma (e.g. falls are more common in young children and road traffic accidents in older children) (4). Shewmon (10) also suggests that children may continue to recover long after adults have reached a plateau, possibly due to their retained potential for further growth and development. They may also be more likely to be offered long-term life support than adults because of the fact that people see them as more 'worthwhile' of the use of resources (4). Some may believe that death is preferable to survival with a severe disability, but Shewmon (10) insists that children and their families adapt better to physical and mental disabilities than most adults do. However, many of these views were difficult to substantiate as children and neonates tend to be excluded from studies on the basis that an accurate and consistent diagnosis of a VS is difficult to make, especially in the youngest children due to a limited capacity to show higher cognitive function (3,14). This is a complex issue with a small amount of applicable research literature available, making it difficult to conclude if any advantage is offered by a younger age. At the other extreme of life, superficially it would appear that there is a relationship between increasing age and mortality in the VS (15), but after adjustment for the severity of the illness and co-morbidity it no longer appears to exist (11,15). Although the age of the patient does not seem to directly contribute to the prediction of outcome from the VS, it may act as a substitute for other important and otherwise unmeasurable cofactors that do (15) such as pre-existing co-morbidity (e.g. cardiovascular disease) and reduced physiological reserve. Therefore, age should still be taken into account in prediction, but not as the deciding factor in where rationing of resources may be an issue and could lead to claims of ageism.

RECOVERY FROM THE VS

There are two dimensions of recovery from the VS (4):

1. Recovery of consciousness

Verified by consistent evidence of self and environment, interaction with others and voluntary behavioural responses.

2. Recovery of function

Characterised by communication, ability to learn and perform adaptive tasks, mobility, self-care and participation in recreational or vocational activities.

Recovery of consciousness may occur without recovery of function, but the converse is never true (4). The VS may be a transient stage in the recovery from coma or it may persist until death (6). The average duration of survival is 2-5 years and mortality for adults has been quoted at 82% at three years and 95% at five years (3,4). Studies have shown that the duration of survival is similar between children and adults (5-7 years), but in infants under one year it is much shorter, with estimates at a maximum of four years (4,8). There have been cases reported of patients being alive in the VS many years after this (48 years is the longest known case) (7), but the probability of prolonged survival in the VS (i.e. longer than fifteen years) has been estimated at less than 1 in 15,000 to 75,000 (4). The cause of death in the VS is most commonly infection (usually of the respiratory or urinary tract) or generalised systemic failure. Underlying comorbidity (such as ischaemic heart disease) and other unknown causes also claim a small proportion of patients but exact figure are not recorded (4).

OTHER ANCILLIARY TESTS

Other tests alone can neither diagnose nor predict if the VS will be permanent. However, when used in conjunction with the clinical examination, they can provide useful supportive information (3).

Imaging Studies (Neuroimaging)

There are no established patterns seen on neuroimaging that have been proven to predict outcome (3,9) and Bates (2) feels that their value in prediction is no better than that of the basic clinical signs. Neuroimaging methods often document lesions so severe and diffuse that awareness is highly improbable, given our current understanding of the anatomy and physiology of the brain. Several studies have documented that patients with serial abnormal scans do not recover consciousness and have progressive brain atrophy (3,7).

Magnetic resonance imaging is proven to be more sensitive than computerized tomography (CT) for detection of traumatic and ischaemic cerebral lesions (9). Kampfl et al. (9) found that although multiple lesions were commonly seen in the VS, additional injuries to specific parts of the brain were of particular importance to its persistence. Patients with lesions of the corpus callosum and dorsolateral upper brainstem had a 214-fold and 7-fold higher probability, respectively, for non-recovery (i.e. VS becoming permanent). However, the study sample size was too small to definitively prove these findings (9,16).

Cerebral Metabolic and Blood Flow Studies

Functional assessment of brain activity has been investigated as an aid to prediction. There is evidence that cerebral blood flow (CBF) is decreased in patients in established VS, with estimates at 10-50% of normal (3,9,17). However, it is accepted that measurement of CBF in the acute phase is of no prognostic significance (3) and it does not reliably predict if recovery is possible.

Cerebral metabolic activity has also been implicated in the prediction of outcome. Using positron emission tomography, a collection of studies (3,9) demonstrated a decreased cerebral metabolic rate of only 40-60% of normal in 20% of adults in permanent VS (3). Unfortunately, the limited power of these studies (due to small sample sizes) means that as yet, there is insufficient evidence to incorporate cerebral metabolic rates or CBF studies into routine practise (3,7,9).

Electrophysiology: EEGs and Evoked Potentials

The transition from coma to the vegetative state is not characterised by obvious EEG changes; it is a clinical diagnosis (2). Most patients in persistent VS show diffuse generalised polymorphic delta or theta activity, which is un-reactive to sensory stimuli. In other patients, alpha activity is the most obvious EEG feature, or some low background activity is all that can be detected (2,3). Epileptiform and seizure activity is rare in VS.

A similar pattern is seen in children although the EEG activity may be of a lower voltage and more discontinuous (3). Before three months, the EEG pattern is termed 'neonatal' and is very different to the EEG seen after this time ('mature' EEG) and throughout the rest of adulthood. This transition is termed encephalisation and is when the child's brain changes from mainly reflex subcortical functioning to cortically mediated cognition. Once this change has taken place, the same prognostic patterns apply to children as to adults, but before this, little information can be gained from EEG due to a lack of research on the topic (7,10). Recovery from the VS may be seen on EEG recordings as decreasing delta and theta activity and reappearance of a reactive alpha rhythm. However, this pattern has also been seen in patients who clinically remain in the VS, suggesting that it is not always predictive of recovery (3).

Sedative, anticonvulsant or anaesthetic drugs may cause depression of brain activity and lead to misdiagnosis on EEG (11). This again emphasises the need to eliminate all reversible causes of coma and to repeatedly assess the patient. However, the technical problems of performing such a measure in a busy intensive care ward with numerous potential sources of electrical interference can cause much of its practical value to be lost (2).

The most sensitive and reliable form of evoked potentials (EPs) in both adults and children are somatosensory evoked potentials (SSEPs) (3). Many studies (2,3,14,18,19) have produced consistent results as to their value but their clinical use is not yet widely adopted due to the belief that it is difficult to obtain accurate and reliable results in the intensive care setting (2,18). The advantage SSEPs have over EEGs is that sedating drugs minimally affect them (18). Many of the studies into SSEPs are not fully blinded, therefore any predictions of death or disability have been criticised as to being, to some extent, a self-fulfilling prophecy. Sleigh et al. (18) carried out a fully blinded study to counteract these claims and to show that SSEPs could be recorded in an ICU where dedicated neurophysiological personnel are not present. They found that bilaterally normal SSEPs were associated with a good outcome (i.e. recovery from the VS) but if they were of reduced amplitude, slowed conduction time or absent altogether, the prognosis was poor. Indeed, if SSEPs were absent bilaterally this carried the worse prognosis, being highly predictive of failure to regain consciousness (i.e. death or permanent VS). However, they were less predictive in traumatic aetiologies due to the structural damage that can ensue during the brain insult. Chen et al. (19) agreed with these findings, giving the poor prognostic factors of low amplitude or absent SSEPs positive predictive values of 100% and 89% respectively. However, as with their EEG findings, whereas negative factors were highly specific, positive ones were not, meaning that although absent or delayed SSEPs accurately predicted a poor outcome, normal SSEPs did not automatically predict a good recovery.

It has been suggested by Yingling et al. (20) that some brainstem EPs can be of predictive value, in particular P300 evoked responses. They suggest that the presence of P300 could indicate the integrity of brain systems that mediate cognitive functions, even in the absence of consciousness or overt behavioural responses. Unfortunately, the work that they have published to show its value was on a very small number of patients and therefore does not have adequate power to alter clinical practise at this time. Its diagnostic value is also limited by the fact that brainstem auditory EPs have been shown to be preserved when SSEPs are absent meaning that the predicted outcome does not alter from performing SSEPs alone - the best outcome possible is survival in the VS or death (3). Therefore, the presence of P300 cannot necessarily be correlated with outcome.

Responses to Stimuli

Motor or eye movements and facial responses such as grimacing in response to various stimuli are commonly seen stereotyped patterns. They are reflexive responses mediated at deep subcortical levels rather than as learned voluntary acts. Therefore, they do not indicate any degree of awareness and the family of the VS patient should be informed of the possibility of their occurrence, to prevent the creation of false hopes (3,7).

Genetic Factors

A small number of studies have suggested that some people may have a genetic predisposition to poor outcome from traumatic injury. The 4 allele of apolipoprotein E (apoE) has been shown to be associated with increased mortality. Sorbi et al. (21) stated that deposition of amyloid -protein (A) in the brain occurs in one third of individuals who die shortly after a severe brain injury. They found that the apoE- 4 allele occurred in a higher frequency in those who did not recover consciousness within a month (entered a persistent VS). For those who did recover, the frequency of the allele was comparable to that of the control population, suggesting a genetic susceptibility to the fatal effect of a head injury. However, their follow up was only for this month, so it is unclear as to whether the frequency of the allele was any higher in those who entered permanent VS. Also, as their study only included 16 patients, their findings have very little statistical power and are therefore inconclusive for the time being.

CONCLUSIONS

Predicting the outcome from the VS is a difficult challenge that, as yet, does not appear to be resolved. Factors mainly influencing prognosis remain etiology and duration. Traumatic brain insults have a better prognosis, nearly half of the patients studied recovered consciousness within six months, compared to only 15% of non-traumatic etiology (4). Patients were also more likely to make a good recovery from traumatic aetiologies in comparison to non-traumatic (4,11). Recovery after a year was rare in both groups (2,4,11). From the work considered, there is a possibility that age may come into the equation. This is largely inconclusive in the younger age groups, but in the older patients, age may act as a substitute for other unmeasurable factors such as comorbidity, and thus should be taken into account when determining prognosis (4). The evidence

is less conclusive in children in comparison to adults, but it appears that a similar pattern is seen in terms of functional recovery. There is evidence to suggest that children may have a better chance of recovering consciousness than adults due to the developmental potential of their brains, especially in non-traumatic etiology (4,10). False predictions of poor outcome should be avoided because this may lead to withdrawal of support in patients with the potential to recover.

Attempts have been made to treat the VS by various techniques, e.g. dopaminergic agonists, direct electrical stimulation of the brain, anticholinergics, GABA agonists, catecholaminergic anatgonists, and serotonergic agonists. However, none of these have been proven to be effective, despite seemingly encouraging preliminary studies (4,7).

Therefore, the evidence would suggest that routine clinical practise in assessment of VS patients should remain repeated clinical examinations to attempt to detect any changes in their awareness. Although criticised for the possible technical difficulties in recording, EEGs and SSEPs should be performed fairly regularly during this period. A CT scan on admission is necessary, as are the standard blood tests, to detect any potentially reversible causes of the coma.

Once a state of permanent VS is reached, little improvement can be expected. Discussion needs to take place with the family to determine the level of treatment that will be given for the duration of their lives; this is mostly preventative (e.g. avoiding contractures, pressure sores, etc). The decision to withdraw artificial nutrition and hydration is not an easy one and patients usually die within ten to fourteen days of acute dehydration and electrolyte imbalance (4,7). In the UK, it remains obligatory to seek a legal ruling to do so unless there is a clear advance directive (5). However, decisions should not be taken before a year has elapsed as the chances of recovery are small but they are a realistic possibility, although the best outcome available is usually severe disability (5,12,13).

Improvement on previous studies is difficult, if not impossible. More work is needed on the subject of prognosis in the VS to allow definitive guidelines to be agreed upon but the same problems of small sample sizes and a low incidence of the condition persists. This will most likely continue to be a problem until a large scale, multicentre trial is organised with the cooperation of major neurological centres throughout the world. This may help to alleviate some of the methodological issues but will be a massive project requiring funding which may not be possible as yet.

The VS is a complex condition that ultimately can only benefit from continued large scale studies into potential treatments and methods of accurately predicting outcome.

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