

## The vegetative state

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The vegetative state may develop suddenly (as a consequence of traumatic or non-traumatic brain injury, such as hypoxia or anoxia; infection; or haemorrhage) or gradually (in the course of a neurodegenerative disorder, such as Alzheimer's disease). Although uncommon, the condition is perplexing because there is an apparent dissociation between the two cardinal elements of consciousness: awareness and wakefulness.<sup>1</sup> Patients in a vegetative state appear to be awake but lack any sign of awareness of themselves or their environment.<sup>w1</sup> Large retrospective clinical audits have shown that as many as 40% of patients with a diagnosis of vegetative state may in fact retain some level of consciousness. Misdiagnosis has many implications for a patient's care—such as day to day management, access to early interventions, and quality of life—and has ethical and legal ramifications pertaining to decisions on the discontinuation of life supporting therapies.<sup>2 w2-w4</sup>

Overall, our understanding of the vegetative state is incomplete. Although we know quite a lot about the neuropathology underlying the vegetative state, our ability to assess (un)consciousness and cognitive function in the clinic is extremely limited, as highlighted by the high rate of misdiagnosis.

### SUMMARY POINTS

The vegetative state is a complex neurological condition in which patients appear to be awake but show no sign of awareness of themselves or their environment

Current clinical methods of diagnosis are limited in scope, evidenced by a high rate (about 40%) of misdiagnosis (that is, patients who are aware are considered to be unconscious)

The main causes of misdiagnosis are associated with a patient's disability (such as blindness), confusion in terminology, and lack of experience of this relatively rare condition

Furthermore, standard behavioural assessments cannot distinguish an aware (that is, minimally conscious) but completely immobile patient from a non-aware patient (one with vegetative state)

In such behaviourally non-responsive patients, functional neuroimaging methods (such as magnetic resonance imaging or electroencephalography) can detect residual cognition and awareness and can even establish two way communication, without requiring any behavioural output from patients

Current guidelines should therefore be modified to include functional neuroimaging as an independent source of diagnostically relevant information

### SOURCES AND SELECTION CRITERIA

This paper is largely based on a personal database of articles from all three authors, including the most recent published work in primary research journals as well as recent and influential reviews and chapters on the subject. We also searched PubMed using the keyword "vegetative state" and the limits "classical article, review and meta-analysis"

### What is the vegetative state and what is it not?

The 2003 guidance from the UK's Royal College of Physicians on diagnosing and managing the permanent vegetative state defines it as "a clinical condition of unawareness of self and environment in which the patient breathes spontaneously, has a stable circulation, and shows cycles of eye closure and opening which may simulate sleep and waking."<sup>3</sup> Three main clinical features define the vegetative state: (a) cycles of eye opening and closing, giving the appearance of sleep-wake cycles (whether the presence of eye opening and closing cycles actually reflects the presence of circadian rhythms is unclear<sup>w5 w6</sup>); (b) complete lack of awareness of the self or the environment; and (c) complete or partial preservation of hypothalamic and brain stem autonomic functions.<sup>3 4</sup> The guidelines from the Royal College of Physicians consider a vegetative state to be persistent when it lasts longer than a month and permanent when it lasts longer than six months for non-traumatic brain injuries and one year for traumatic brain injuries.<sup>3</sup> Guidelines published in the United States, however, consider that for non-traumatic brain injury a permanent vegetative state exists after only three months.<sup>4</sup>

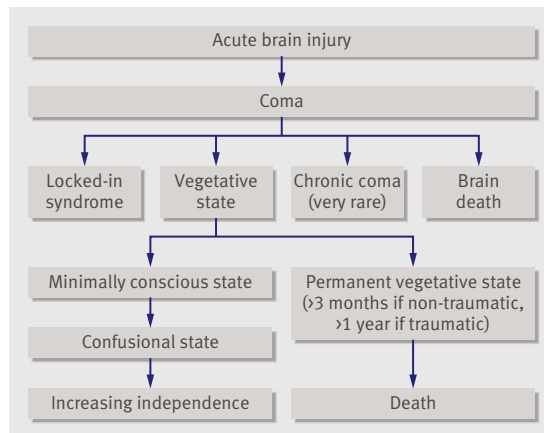
Although both the persistent and the permanent vegetative states are often abbreviated to "PVS," authors of a letter in the *BMJ* in 2000 suggested that to avoid confusion the abbreviation should be used exclusively to indicate a permanent vegetative state.<sup>w7</sup> The American Congress of Rehabilitation Medicine suggested that the cause of injury (traumatic, anoxic) as well as the time elapsed since onset of the condition should be documented, as both are important for prognosis.<sup>w8</sup>

Experts have suggested that the vegetative state should be seen as part of a continuous spectrum of conditions, often referred to as disorders of consciousness, in which someone's wakefulness and/or awareness are impaired after severe brain injury (figure, table 1).<sup>5 6</sup> This suggestion is consistent with the idea that awareness and unawareness are part of a continuum, and it highlights the

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- ▶ Huntington's disease (*BMJ* 2010;340:c3109)



Flow chart of cerebral insult and coma. Adapted from Laureys et al, 2004<sup>w9</sup>

**Table 1 | Consciousness and motor behaviour characteristics in patients with disorders of consciousness and locked-in syndrome**

Condition	Consciousness		Motor behaviour characteristics
	Sleep-wake cycles	Awareness	
Coma	No	No	No purposeful behaviour
Vegetative state	Yes	No	No purposeful behaviour
Minimally conscious state	Yes	Partial, fluctuating	Inconsistent but reproducible purposeful behaviour
Locked-in syndrome	Yes	Yes	Yes, but limited to eye movements (depending on lesion)

importance of differentiating the vegetative state from other related neurological conditions that may also follow catastrophic brain injury.

**Coma**

Coma is a condition of unresponsiveness in which patients lie with their eyes closed, do not respond to attempts to arouse them, and show no evidence of awareness of self or of their surroundings.<sup>7</sup> Patients lack not only signs of awareness (similar to vegetative state) but also wakefulness (unlike vegetative state) regardless of how intensely they are stimulated. Patients typically either recover or progress to a vegetative state (that is, they show signs of wakefulness) within four weeks.<sup>3</sup> Irreversible coma with absent brainstem reflexes indicates brain death, which is not the same as a vegetative state.<sup>8</sup>

**Minimally conscious state**

The minimally conscious state is a condition in which patients appear not only to be wakeful (like vegetative state patients) but also to exhibit inconsistent (fluctuating) but reproducible signs of awareness (unlike patients with vegetative state).<sup>9</sup> Like the vegetative state, the minimally conscious state may be transitory and precede recovery of communicative function or may last indefinitely.

**Locked-in syndrome**

Locked-in syndrome (or pseudocoma), although not a

disorder of consciousness, may be confused with vegetative state. Patients with locked-in syndrome are both awake and aware, yet they are entirely unable to produce any motor output or they have an extremely limited repertoire of behaviours (usually vertical eye movement or blinking).<sup>w10 w11</sup>

**What causes the vegetative state?**

In terms of neuropathology, the vegetative state is mostly marked by cortical or white matter and thalamic, rather than brain stem, injury. A review of the evidence available up until 1994 highlighted the fact that traumatic injury was found to be associated with diffuse damage to subcortical white matter (or diffuse axonal injury). Cases of non-traumatic injury, on the other hand, were found to have extensive necrosis in the cerebral cortex, almost always associated with thalamic damage.<sup>10</sup>

In a more recent survey of patients with brain injury (n=49), 35 (71%) patients had traumatic brain injury, of whom 25 (71%) had severe diffuse axonal injury and 7 (20%) had major injury to the cerebral cortex.<sup>11</sup> Among the 35 patients, the thalamus seemed to be abnormal in 28 (80%) and damage to the brain stem was present in only 5 (14%). In the 14 (29%) patients with non-traumatic injury, 9 (64%) cases presented with diffuse neocortical damage; in all 14 cases a profound and diffuse neuronal loss was apparent in the thalamus and hippocampus. Overall, these lesions effectively render a structurally intact cortex unable to function by destroying the connections between cortical areas via the thalamus, as well as afferent and efferent cerebral connections.

**What affects prognosis in patients with a diagnosis of vegetative state?**

Three major factors affect the prognosis of patients with vegetative state: time spent in the vegetative state, age, and type of brain injury.

**Time spent in the vegetative state**

A study of 140 patients showed that time spent in a vegetative state is negatively correlated with the chances of recovering independence and consciousness and positively correlated with the probability of remaining in a vegetative state.<sup>12</sup> The role of time in prognosis was confirmed by a large review of 603 adult published cases,<sup>13</sup> from which it was estimated that the chance of regaining independence at one year after injury steadily decreased with time from 18% (one month in the vegetative state), to 12% (three months), and 3% (six months). Similarly, the chance of recovering consciousness at one year also decreased, from 42% to 27% and 12% respectively. The chances of remaining in the vegetative state at one year after injury were estimated to increase from 19% to 35% and 57% respectively.

**Age**

Younger patients show better recovery rates.<sup>13</sup> In one report, for example, the rates of recovering independence at one year decreased from 21% for patients below 20 years old to 9% for patients between 20 and 39 years old and 0% for patients above 40 years.<sup>12</sup>

**ADDITIONAL EDUCATIONAL RESOURCES**

- NHS Choices ([www.nhs.uk/Conditions/Vegetative-state/Pages/Introduction.aspx](http://www.nhs.uk/Conditions/Vegetative-state/Pages/Introduction.aspx))—NHS information about the vegetative state
- Royal College of Physicians. The vegetative state: guidance on diagnosis and management. 2003. <http://bookshop.rcplondon.ac.uk/contents/47a262a7-350a-490a-b88d-6f58bbf076a3.pdf>.
- Scholarpedia ([www.scholarpedia.org/article/Vegetative\\_state](http://www.scholarpedia.org/article/Vegetative_state))—Web based encyclopaedia that gives a comprehensive, peer reviewed, overview of definitions, diagnostic criteria, and recent research on vegetative state and related disorders of consciousness
- Headway ([www.headway.org.uk/Core/DownloadDoc.aspx?documentID=446](http://www.headway.org.uk/Core/DownloadDoc.aspx?documentID=446))—Fact sheet on coma from the brain injury association Headway, a charity providing help and support to people affected by brain injury

**Type of brain injury**

Traumatic brain injuries are associated with better outcomes at one year than non-traumatic injuries, in terms of recovery of independence (24% v 4%) and recovery of consciousness (52% v 13%).<sup>3 4 13</sup> Once permanent vegetative state is diagnosed, the chances of recovery are considered to be “extremely low,”<sup>4</sup> with any further recovery being “exceedingly rare, and almost always involving severe disability”<sup>13</sup>; and although cases of late recovery have been reported,<sup>w12-w14</sup> a precise estimate of the likelihood of further recovery remains difficult to formulate. This is mainly because these cases are often difficult to verify, and when a set of 30 cases claiming late recovery were reassessed by the Multi-Society Task Force on PVS, evidence of conscious awareness could be detected in half of them well before the boundary for a diagnosis of permanent vegetative state.<sup>13 14</sup>

**How is the vegetative state diagnosed?**

No tool exists for quantifying the extent of consciousness. Differentiating between awareness and non-awareness ultimately relies on a pragmatic principle that someone is conscious if they can indicate so. Cur-

rently, the diagnosis of the vegetative state is based on two main sources of information: a detailed clinical history and careful (but subjective) observation of the patient’s spontaneous and elicited behaviour. Clinical assessments involve repeated examinations at different times of the day because patients who are not in a vegetative state may have alternating periods of awareness and unawareness (and a single examination cannot exclude a state of minimal consciousness) as well as circadian oscillations in levels of wakefulness. Examinations aim to uncover evidence of (a) awareness of the self or the environment; (b) sustained, reproducible, purposeful, or voluntary response to visual, olfactory, auditory, tactile, or noxious stimuli; and (c) comprehension of language or expression. If evidence of these exists, the patient is considered to be (minimally) aware. If meaningful “object use” (such as appropriate use of a spoon or comb) or consistent communication can also be established, then the patient is considered to have emerged from a minimally conscious state to a condition of severe disability (table 2).<sup>9</sup> However, if no evidence of awareness can be found, the patient is considered to be “not aware” and therefore in a vegetative state.

Although several protocols exist for conducting behavioural assessments (articles by Giacino et al and Majerus et al provide an overview<sup>w15 w16</sup>), they differ greatly in their ability to detect consciousness because of the number of domains (such as arousal and vision) assessed and the thoroughness of the assessment. Indeed, a recent study of 60 patients compared on three assessment techniques reported that the Glasgow coma scale<sup>w17</sup> classified as vegetative several patients who showed signs of consciousness according to other behavioural scales.<sup>15</sup> The Full Outline of UnResponsiveness (FOUR)<sup>w18</sup> reclassified 13% of the supposedly vegetative patients as minimally conscious, and the coma recovery scale-revised (CRS-R)<sup>w19</sup> reclassified an additional 28% of the patients as minimally conscious. The main discrepancy between scales seems to relate to their different focus on oculomotor behaviour, with the FOUR and CRS-R protocols testing a greater variety of visual behaviours. For example, in all the patients reclassified by the CRS-R protocol, visual fixation was the key behaviour indicating awareness.

**Does misdiagnosis of the vegetative state occur?**

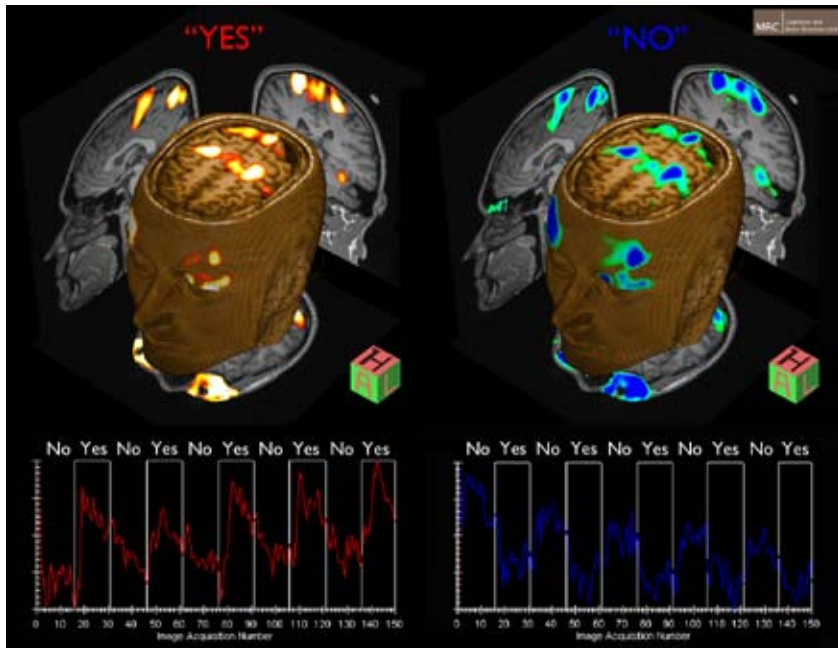
According to accumulating evidence from retrospective clinical audits<sup>2 16</sup> and comparisons of alternative behavioural assessment techniques,<sup>17 18</sup> misdiagnosis of minimally conscious patients as being in a vegetative state is not uncommon. In particular, although some studies have reported relatively low rates of misdiagnosis (18%<sup>w20</sup>), most studies seem to converge, across time and geographical location, on an approximate rate in excess of 40% (37%,<sup>16</sup> 41%,<sup>18</sup> 43%,<sup>2</sup> 45%<sup>19</sup>). Errors in diagnosis may result from lack of skill or training in the assessment of patients with catastrophic brain injury, limited knowledge of this relatively rare condition, and confusion in terminology.<sup>16 20</sup>

Two main problems seem to underlie misdiagnosis. Firstly, behavioural assessments of awareness present many complexities. For example, patients with physical

**Table 2 | Differential diagnosis in severe brain injury survivors**

Condition	Definition	Main clinical characteristics
Coma	Unarousable state of unresponsiveness	Absence of eye opening (even after intense stimulation) No evidence of awareness of the self or environment Condition protracted for more than one hour
Vegetative state	Wakefulness accompanied by the absence of any sign of awareness	Presence of eye opening and closing Absence of any reproducible purposeful behaviour including (a) no evidence of non-response to sensory stimulation; (b) no evidence of awareness of the self or the environment; (c) no evidence of language comprehension or expression
Minimally conscious state	Wakefulness accompanied by inconsistent but reproducible signs of awareness	Presence of eye opening and closing Presence of inconsistent but reproducible purposeful behaviour including (any of) (a) non-reflexive response to sensory stimulation; (b) awareness of the self or the environment; (c) language comprehension or expression Lack of functional communication or object use
Locked-in syndrome	Impairment in the production of voluntary motor behaviour	Presence of eye-coded communication Preserved awareness Complete or partial inability to produce motor behaviour





The ability of novel brain imaging technologies, such as functional magnetic resonance imaging, to covertly detect signs of consciousness and residual cognition can contribute to correctly diagnosing the vegetative state

disability may not be able to respond to stimulation—something that was true in all misdiagnosed cases in a large retrospective study of 97 patients with profound brain damage.<sup>2</sup> Sensory impairments (particularly in the visual domain) can also mask the presence of awareness,<sup>16–20</sup> a factor that has been reported as underlying as many as 65% of misdiagnoses.<sup>2</sup> Other acquired conditions, such as hydrocephaly,<sup>3 w21</sup> can also mask the presence of awareness. In addition, patients in a minimally conscious state may display inconsistent behaviour, making it difficult to interpret their responses, and they may be not aware for protracted intervals, making it difficult to interpret failure to respond.<sup>3</sup>

Secondly, there is a conceptual problem in the logic of establishing “lack of awareness”<sup>21–22</sup>: absence of evidence (of awareness) is taken as evidence of absence (of awareness). Consequently, on the basis of the current clinical standards, patients who are aware but non-responsive cannot be distinguished from non-aware (vegetative) patients.<sup>23–24</sup> Clinically, this flaw in logic introduces a category of aware but non-responsive patients for whom a diagnosis of vegetative state is technically appropriate

#### QUESTIONS FOR FUTURE RESEARCH

What proportion of patients with supposed vegetative state can show a state of consciousness by using functional neuroimaging methods?

What proportion of behaviourally non-responsive patients can convey yes/no answers by wilful modulation of brain activity?

Do patients with disorders of consciousness have a “stream of thoughts”? Do they suffer? Do they understand their circumstance? What is their quality of life?

Can more sophisticated brain computer interfaces be used to allow these patients to interact with their environment and regain some level of communication and autonomy?

(that is, they show no signs of awareness) but incorrect (in fact, they are aware).<sup>21–22</sup>

#### Is there a place for brain imaging as a diagnostic tool?

In recent years, techniques such as positron emission tomography, functional magnetic resonance imaging, and electroencephalography have been used to try to assess residual brain function and consciousness in vegetative patients without relying on motor behaviour. Neuroimaging studies in patients in a vegetative state have shown a consistent reduction in brain metabolism of as much as 50%<sup>w22</sup> and reduced basal resting state activity.<sup>25</sup> In addition, unexpected levels of residual cognitive function (such as processing of linguistic and self referential stimuli) are present in both minimally conscious patients and patients in a vegetative state.<sup>26–27</sup> In some of these cases, high level functions (such as learning and actively maintaining information through time) are present,<sup>28–30</sup> as are awareness<sup>23–24</sup> and the ability to communicate solely by modulation of brain activity.<sup>23</sup>

The Multi-Society Task Force on PVS states, however, that “neurodiagnostic” tests, although recognised as “providing useful information when used in conjunction with clinical evaluation” are believed to be unable, alone, to “either confirm the diagnosis of vegetative state . . . or predict the potential for recovery of awareness.”<sup>4</sup> Although we agree that functional neuroimaging cannot confirm a diagnosis of vegetative state, it is increasingly clear that functional neuroimaging can be used to rule out a diagnosis of vegetative state and may even yield information about prognosis. Indeed, limited data on prognosis show that quantitative measurements of brain activity—in particular, activations beyond primary sensory cortices—are positively correlated with recovery from the vegetative state.<sup>26–28 w23</sup>

#### Conclusion

Disorders of consciousness remain challenging to manage because of our superficial understanding of the phenomenon of consciousness and its neural mechanisms. Two main strategies seem promising for reducing the consistently high misdiagnosis rate. Firstly, behavioural assessments need to be conducted more thoroughly and by trained staff (a neurologist or another healthcare professional who has been trained to use the formalised assessments mentioned previously).<sup>2–16 18–20</sup> Secondly, we believe that the inclusion of recommendations for the use of functional neuroimaging techniques in revised guidelines will increase the detection of covert signs of awareness in the very circumstances susceptible to misdiagnosis. In addition, these techniques can be used to explore the degree of mental life possible after severe brain injury,<sup>w24</sup> thus tackling the medically and ethically important question “what is it like to be in a vegetative state?” In a minority of cases, these techniques may even allow the patients to interact with their environment and to some extent let their voice be heard.<sup>23</sup>

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**ANSWERS TO ENDGAMES, p 307.** For long answers go to the Education channel on [bmj.com](http://bmj.com)

**ANATOMY QUIZ**

**T2 weighted axial magnetic resonance image of the brain**

- A Right medial rectus muscle
- B Right side of the pons
- C Left lateral rectus muscle
- D Basilar artery
- E 4th ventricle

**STATISTICAL QUESTION**

**Relative risks and confidence intervals**

Answers a, b, and d, are true, whereas c is false.

**ON EXAMINATION QUIZ ICD-10 classification**

False.

More questions on this topic are available from [www.onexamination.com/endgames](http://www.onexamination.com/endgames) until midnight on Wednesday.

**CASE REPORT**

**Recurrent vomiting and lethargy in an infant—just another viral illness?**

- 1 The differential diagnoses are metabolic disorder, neglect, coeliac disease, viral gastroenteritis, hypothyroidism, and HIV infection.
- 2 Hyperammonaemia is responsible for this patient's clinical picture.
- 3 The raised plasma concentration of ammonia and respiratory alkalosis suggest a urea cycle defect caused by inherited defects of enzymes responsible for the metabolism of waste nitrogen. Further tests showed raised urinary orotate and plasma glutamine and low plasma citrulline, consistent with a diagnosis of ornithine transcarbamylase (OTC) deficiency.
- 4 Hyperammonaemia should be managed with nil by mouth; infusion of 10% dextrose and sodium benzoate; arginine supplementation; and regular monitoring of plasma ammonia, glucose, urea, and electrolytes in addition to blood gases.