Original Study

The Vegetative State: Prevalence, Misdiagnosis, and Treatment Limitations

Willemijn S. van Erp MD a,b,*, Jan C.M. Lavrijsen MD, PhD a, Pieter E. Vos MD, PhD c, Hans Bor BSc a, Steven Laureys MD, PhD b,d,e, Raymond T.C.M. Koopmans MD, PhD a,f

a Department of Primary and Community Care, Centre for Family Medicine, Geriatric Care and Public Health, Radboud University Medical Centre, Nijmegen, The Netherlands
b Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liège, Liège, Belgium
c Department of Neurology, Singeland Ziekenhuis, Doetinchem, The Netherlands
d University Hospital of Liège, Liège, Belgium
e Belgian Funds for Scientific Research, Belgium
f Waalboog Foundation, Joachim and Anna, Centre for Specialised Geriatric Care, Nijmegen, The Netherlands

Keywords:
Long-term care
vegetative state
ethics
acquired brain injury
rehabilitation

A B S T R A C T

Introduction: Patients in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) open their eyes spontaneously, but show only reflexive behavior. Although VS/UWS is one of the worst possible outcomes of acquired brain injury, its prevalence is largely unknown. This study’s objective was to map the total population of hospitalized and institutionalized patients in VS/UWS in the Netherlands: prevalence, clinical characteristics, and treatment limitations.

Methods: Nationwide point prevalence study on patients in VS/UWS at least 1 month after acute brain injury in hospitals, rehabilitation centers, nursing homes, institutions for people with intellectual disability, and hospices; diagnosis verification by a researcher using the Coma Recovery Scale-revised (CRS-r); gathering of demographics, clinical characteristics, and treatment limitations.

Results: We identified 33 patients in VS/UWS, 24 of whose diagnoses could be verified. Patients were on average 51 years old with a mean duration of VS/UWS of 5 years. The main etiology was hypoxia sustained during cardiac arrest and resuscitation. More than 50% of patients had not received rehabilitation services. Most were given life-sustaining treatment beyond internationally accepted prognostic boundaries regarding recovery of consciousness. Seventeen (39%) of 41 patients presumed to be in VS/UWS were found to be at least minimally conscious.

Conclusions: Results translate to a prevalence of 0.1 to 0.2 hospitalized and institutionalized VS/UWS patients per 100,000 members of the general population. This small figure may be related to the legal option to withhold or withdraw life-sustaining treatment, including artificial nutrition and hydration. On the other hand, this study shows that in certain cases, physicians continue life-prolonging treatment for up to 25 years. Patients have poor access to rehabilitation and are at substantial risk for misdiagnosis.

The vegetative state, recently renamed “unresponsive wakefulness syndrome” (VS/UWS),1 is one of the worst possible outcomes of acquired brain injury. A patient in VS/UWS opens his or her eyes spontaneously, but shows no signs of consciousness; only reflexive responses to the outside world are seen.2,3 Although often a transitional state in the process of recovery,4 certain patients remain in VS/UWS for the rest of their lives, sometimes decades after the causative event.

The differential diagnosis of VS/UWS includes the locked-in syndrome in which the patient is fully conscious while incapable of speech and most motor reactions due to near-complete paralysis,5,6 and the minimally conscious state (MCS), characterized by at least one sign of consciousness but absence of functional communication

The authors declare no conflicts of interest.

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). The study sponsors and funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

This study was funded by the Stichting Beroepsopleiding Huisartsen (SBOH) (WSvE, JCML); and the Belgian Funds for Scientific Research (FRS), European Commission, McDonnell Foundation, and University of Liège (SL).

* Address correspondence to Willemijn S. van Erp, MD, Department of Primary and Community Care, 117, Centre for Family Medicine, Geriatric Care and Public Health, Radboud University Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

E-mail address: willemijn.vanerp@radboudumc.nl (W.S. van Erp).

http://dx.doi.org/10.1016/j.jamda.2014.10.014

1525-8610/© 2015 AMDA – The Society for Post-Acute and Long-Term Care Medicine.
and functional use of objects. Recently argued to distinguish patients who reproducibly follow commands (MCS+) from those who do not (MCS−).

Although the neurophysiological substrates of disorders of consciousness are steadily being unravelled, their epidemiology remains unclear. In many countries, including the United States and Great Britain, the prevalence of VS/UWS is unknown. A recent systematic review of prevalence studies on VS/UWS yielded 14 publications with a wide variation in both outcome (0.2–6.1 patients per 100,000 members of the general population) and methodological quality.

Uncertainty about the exact number of people in a condition referred to as “a fate worse than death” not only compromises our scientific picture, it also can be a barrier to the provision of the specialized health care these patients and their families need. In 2003, a Dutch prevalence study resulted in what appears to be the lowest reported prevalence of VS/UWS in the world: 0.2 patients per 100,000 members of the population. However, it targeted the nursing home population exclusively and verified only a small subset of cases, whereas it has been shown that up to 43% of patients presumed to be in VS/UWS turn out to be at least in MCS when examined with a validated assessment tool.

This article describes a point prevalence study of VS/UWS carried out nationwide in hospitals, nursing homes, hospices, facilities for people with intellectual disability (ID), and rehabilitation centers in the Netherlands.

**Methods**

The Netherlands is inhabited by 16.7 million people and has a population density of 401 people per square kilometer (in comparison, the United States has a population density of 33.7 per square kilometer). Medical aid, including long-term care, is available for all citizens and reimbursed through a dually financed insurance system. Nursing homes are staffed by specialized medical doctors, called elderly care physicians.

In the last week of April 2012, we contacted medical directors from all of the 635 nursing homes (merged in 187 organizations); 20 rehabilitation centers; 90 hospitals with an intensive care unit, neurology, and/or neurosurgery ward; and 70 hospices, plus the 27 members of the Dutch Association of ID Physicians via e-mail. The e-mail provided the internationally established diagnostic criteria for VS/UWS. The addressee was asked whether any patients with this diagnosis at least 1 month after acute brain injury (eg, hypoxia, stroke, trauma) were present within the population under the responsibility of the medical staff on May 1, 2012. Replies were given by e-mail. If a missing response could not be retrieved by telephone, the institution or physician was considered a nonresponder.

Representatives, mostly family members, of all patients reported received an information letter about the study and were asked for written informed consent. On permission, one researcher (WvE) assessed the level of consciousness by means of the Coma Recovery Scale-revised (CRS-r), a validated instrument for bedside determination of the level of consciousness in the post-acute setting. Staff and family were invited to the assessment. Any additional behavior was reported by medical staff or families. In 24 of 44 individuals, CRS-r assessment confirmed MCS+ in both patients. Combined with the 7 cases in which we obtained no consent, this resulted in 9 unverified cases. Thus, the diagnosis could be verified in 44 patients. Six patients had recently had infections, seizures, or other events possibly influencing level of consciousness, 15 were on medication with sedative side-effects, and 13 patients were assessed within 1 hour after the administration of artificial nutrition.

In 24 of 44 individuals, CRS-r assessment confirmed the diagnosis of VS/UWS. In 3 other cases, the treating physician expressed doubts about the diagnosis. One of these patients was found to be in MCS−, the other 2 were conscious, as demonstrated by the ability of functional use of objects and/or functional communication
Signs of Consciousness in Patients With Doubtful Diagnosis

Table 1

Patient Characteristics

(Table 1). Seventeen of 41 patients with a reported clinical diagnosis of VS/UWS (39%) showed signs of consciousness: 11 were in MCS−, 4 in MCS+, and 2 were conscious (Table 2). All signs of consciousness were detected by means of the CRS-r, with the exception of one patient who reproducibly showed a distinctive facial expression and vocalization when presented with an ice cream. The other patients' conscious behavior had not been witnessed by staff before (eg, communication only with a nephew) or had been seen but not been recognized as a sign of consciousness (eg, visual following of a mirror). The proportion of families who agreed with the diagnosis of VS/UWS was nearly the same for misdiagnosed and confirmed VS/UWS patients (45% versus 50%, respectively).

The 24 verified and additional 9 potential cases resulted in a total of 24 to 33 hospitalized and institutionalized patients in VS/UWS in the Netherlands, or 0.1 to 0.2 for every 100,000 members of the general Dutch population on May 1, 2012.

![Fig. 1. Flowchart showing results of prevalence inquiry and verification.](image)

**Table 1**: Signs of Consciousness in Patients With Doubtful Diagnosis

<table>
<thead>
<tr>
<th>Treating Physician's Diagnosis</th>
<th>Consensus; Agreement on Diagnosis Between Staff and Proxies</th>
<th>Coma Recovery Scale-revised</th>
<th>Structured Observation</th>
<th>Researcher's Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doubt</strong></td>
<td>No: proxies consider behaviour to be reflexive, staff has doubts</td>
<td>Object manipulation</td>
<td>Manipulates poker chips exclusively No additional findings MCS−</td>
<td>Conscious</td>
</tr>
<tr>
<td><strong>Doubt</strong></td>
<td>No: proxies and physical therapist consider movements to be nonreflexive, physician has not witnessed this</td>
<td>Reproducible movement to command, functional use of object (spoon) only on request of proxy</td>
<td>No additional findings</td>
<td>Conscious</td>
</tr>
<tr>
<td><strong>Doubt</strong></td>
<td>No: proxies experience functional verbal communication, staff has not witnessed this</td>
<td>Functional communication only with nephew</td>
<td>No additional findings</td>
<td>Conscious</td>
</tr>
</tbody>
</table>

Basic characteristics are shown in Table 3. Notably, half of the total patient group (12/24) was in VS/UWS due to postanoxic encephalopathy following cardiac arrest and resuscitation. Trajectory was present in 8 cases (33%); 5 were cuffed, 3 noncuffed. This group had sustained the causative injury relatively recently (mean 1 year, 8 months) when compared with the group without trajectory (mean 6 years, 8 months). All patients received ANH via percutaneous endoscopic gastrostomy, except for one patient with a nasogastric tube. Her physicians had decided to refrain from new medical interventions soon after the causative event, 3 years before. None of the individuals were on respiratory support, 7 (29%) had a urinary catheter. There were no pressure sores.

Four patients (17%) were within internationally accepted prognostic boundaries, this is, 3 months after nontraumatic and 12 months after traumatic causes. The other 20 patients had been in VS/UWS for on average 6 years (SD 6 years 2 months); 3 nontrauma for 3 to 12 months, 9 for 1 to 5 years, 5 for 5 to 10 years, and 3 for more than 10 years. One patient had suffered traumatic brain injury at age 18, and was now 43.

None of the patients had a known advanced care directive. The treatment goal was defined as “palliative” (ie, aimed at quality of life, may include life-prolonging therapies) in 13 patients, “curative” (ie, aimed at recovery of consciousness) in 5 patients, “symptomatic” (ie, aimed at quality of life, excluding life-prolonging therapies) in 3, and “other” in 3 patients. Treatment limitations were in place in 19 patients (79%): 19 were not to be resuscitated, 16 were not to be intubated, 11 were not to be readmitted to the intensive care unit, and 9 were not to be readmitted to hospital in general. In 4 patients, the treating physician expressed the intention to withdraw medical treatment, including ANH. On the other hand, 4 of the aforementioned patients who were beyond chances of recovery had no treatment limitations at all.

On the study date, 2 patients were still in hospital. Of the remaining 22 individuals admitted to long-term care facilities, only 10 (46%) were or had been enrolled in either a specialized (ie, sensory stimulation therapy25) or regular rehabilitation program.

**Discussion**

To the best of our knowledge, this is the first prevalence study on VS/UWS carried out nationwide in all health care sectors and aiming at 100% diagnosis verification by means of the CRS-r. We found an overall prevalence of 0.1 to 0.2 hospitalized and institutionalized VS/UWS patients per 100,000 inhabitants. As mentioned, a Dutch prevalence study performed in 2003 yielded a similar figure, although this was limited to the nursing home population and with diagnosis verification in only 9.4% of cases.14 When comparing the 2003 results with the present, the most striking difference is in etiology. Whereas stroke accounted for 47% of VS/UWS cases 10 years ago, in the current population it is the causative injury in only 13%. Instead, the major cause of VS/UWS (50% of patients) is now hypoxic brain injury, whereas in 2003, this was the etiology in merely 23%. Notably, none of the patients had any reported pressure sores. This can be seen as a mark of the level
of care and caring provided to the patients in these settings in the Netherlands.

Considering methodological factors and the shortage of reliable figures from other countries, the prevalence of VS/UWS in the Netherlands seems relatively low. This may be attributable to end-of-life decisions in the acute phase of severe brain injury, as well as in post-acute and long-term care settings. In the 1990s, an ethical, legal, and medical framework was established in the Netherlands stating that life-sustaining treatment, including ANH, for the sole purpose of prolonging VS/UWS beyond chances of recovery of consciousness is medically futile and violates human dignity. In practice, withdrawal of ANH is allowed beyond 3 to 6 months after nontraumatically and 12 months after traumatically induced VS/UWS. The decision to withhold or withdraw medical treatment is made by the physician. Still, in 20 of 24 patients in our study, life-sustaining treatment was continued beyond these prognostic boundaries. In other words, despite the legal option of ANH withdrawal, Dutch doctors do continue treatment, in certain cases for more than 25 years. The finding that many families disagree with the diagnosis of their loved one in VS/UWS is likely to influence medical decision-making. Earlier publications suggest the absence of advanced care directives to play a crucial role in these processes, as well.

Remarkably, one of the patients in this study was reported to have emerged from VS/UWS 10 months after the occurrence of nontraumatic brain injury. Recent publications show that the aforementioned prognostic boundaries may be outdated. Our methods, however, were not designed to assess VS/UWS prognosis. Another unexpected finding was the absence of children in our population. It might be that parents prefer to care for them at home, organizing professional support through the system of personal care budgets provided by the Dutch government.

In the Netherlands, clinical rehabilitation for disorders of consciousness is reimbursed only for patients up to the age of 25. Older individuals are sometimes accepted to a similar program in 1 of 2 dedicated nursing homes, which receive no financial coverage from health insurance companies and therefore have limited capacity. The consequences are reflected in our study: 54% of patients had been admitted directly to a long-term care facility without going through any form of rehabilitation. Although the effects of specialized rehabilitation for disorders of consciousness have not been established in a randomized controlled setting, the fact that a country allows cessation of treatment without enabling patients to fully explore their means of recovery raises questions.

Seventeen (39%) of 44 patients considered to be in VS/UWS turned out to be in MCS or were even conscious when examined with the CRS-r. For the first time, diagnostic accuracy of VS/UWS has been examined in long-term care facilities. Our results correspond to previous studies on the diagnostic accuracy of VS/UWS in hospitals and rehabilitation centers. The difference between VS/UWS and MCS is of considerable clinical relevance. Patients in MCS have a better chance of recovery than VS/UWS patients and appear to process emotional, auditory, and nociceptive stimuli in a way very similar to that of healthy individuals. Underestimating their level

<table>
<thead>
<tr>
<th>Treating Physician’s Diagnosis</th>
<th>Consensus: Agreement on Diagnosis Between Staff and Proxies</th>
<th>Coma Recovery Scale-revised</th>
<th>Structured Observation</th>
<th>Researcher’s Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS/UWS Yes</td>
<td>Visual following</td>
<td>No additional findings</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS Yes</td>
<td>Visual following</td>
<td>No additional findings</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS Yes</td>
<td>Visual following</td>
<td>No additional findings</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS Yes</td>
<td>Visual following</td>
<td>Laughs appropriately during stand-up comedian’s conference on TV</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS Yes</td>
<td>Reflexive behavior</td>
<td>Smiles in response to ice cream, screams when ice cream is removed, smiles when returned 4/4 trials</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS Yes</td>
<td>Localization of noxious stimuli</td>
<td>Fumbles with sheet</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS No: proxies experience eye contact</td>
<td>Visual following</td>
<td>No additional findings</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS No: proxy experiences functional communication by means of sights and facial expression</td>
<td>Visual following</td>
<td>No additional findings</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS No: proxies experience eye contact</td>
<td>Visual following, automatic motor response</td>
<td>No additional findings</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS No: proxies and nurses consider ball catching nonreceptive</td>
<td>Object localization (reaching), localization of noxious stimuli</td>
<td>Catches a ball thrown horizontally from 2 m distance</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS No: paramedics consider reactions to visual stimuli to be nonreceptive</td>
<td>Object recognition, automatic motor response</td>
<td>No additional findings</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS Yes</td>
<td>Reproducible movement to command, visual following, object manipulation, intentional communication when asked for by proxy</td>
<td>No additional findings</td>
<td>MCS–</td>
<td></td>
</tr>
<tr>
<td>VS/UWS Yes</td>
<td>Reproducible movement to command, visual fixation</td>
<td>Visual fixation on children’s picture</td>
<td>MCS+</td>
<td></td>
</tr>
<tr>
<td>VS/UWS No: proxies consider smiles to be nonreceptive</td>
<td>Reproducible movement to command, object recognition</td>
<td>Shakes researcher’s hand</td>
<td>MCS+</td>
<td></td>
</tr>
<tr>
<td>VS/UWS No: proxies experience eye contact</td>
<td>Reproducible movement to command, object recognition</td>
<td>No additional findings</td>
<td>MCS+</td>
<td></td>
</tr>
<tr>
<td>VS/UWS Yes</td>
<td>Consistent movement to command, object recognition, functional use of object (toothbrush), functional communication when asked for by proxy</td>
<td>No additional findings</td>
<td>Conscious</td>
<td></td>
</tr>
<tr>
<td>VS/UWS No: proxies and speech therapist report functional use of objects and command following, unwatched by physician</td>
<td>Systematic movement to command, object localization (reaching), functional use of objects (spoon, toothbrush) only on request of speech therapist</td>
<td>No additional findings</td>
<td>Conscious</td>
<td></td>
</tr>
</tbody>
</table>

MCS–, minimally conscious state in which patients do not reproducibly follow commands; MCS+, minimally conscious state in which patients reproducibly follow commands; VS/UWS, vegetative state/unresponsive wakefulness syndrome.
of consciousness may have serious consequences in terms of prognosis, access to rehabilitation, analgesia, and end-of-life decisions. In some cases we assessed, subtle signs of consciousness seem to have gone unnoticed by staff. This is particularly understandable when it comes to eye tracking or responses occurring only in reaction to very specific stimuli. In others, conscious behavior was wrongfully labeled reflexive, such as in the patient who had for years been able to catch a ball. Only one of the institutions we visited used a specific scale for level of consciousness assessment in the post-acute phase: a nursing home with a specialized rehabilitation ward, where the Western Neuro Sensory Stimulation Profile was administered. Unfamiliarity with MCS as a distinct clinical condition and the rareness of prolonged disorders of consciousness may give rise to misdiagnosis as well.

There are limitations to this study. Although high response rates were obtained from hospitals, nursing homes, and rehabilitation centers, we cannot ignore the possibility of underreporting, especially from hospices and facilities for people with ID. Missing responses from these sectors could not be pursued, because many Dutch hospitals are staffed by consultants, and because of the absence of a central registry of ID facilities. It is also imaginable that some negative responses were incorrect; that is, respondents based their reply on incomplete information. If this were the case, the actual number of patients appears to be too small for nonspecialized health care institutions to gather and retain adequate experience and expertise.

We suggest the installation of a readily accessible network of experts providing on-site diagnostic, prognostic, and therapeutic advice to staff, monitoring level of consciousness by means of the CRS-r and complementary diagnostics. A network like this also could ensure liaison between hospitals, rehabilitation centers, and nursing homes and guide families along the process. Future research should concern patients being cared for at home and in ID facilities, long-term outcomes, as well as factors contributing to the apparently low prevalence of VS/UWS in the Netherlands. Until medical science finds a cure for the severest outcomes of acquired brain injury, this seems to be the least that could, and should, be offered to patients with prolonged disorders of consciousness and their families.

Acknowledgments

We thank the SBOH for making this research project possible. Our gratitude also goes out to all cooperating physicians, and to the patients and their families who were involved in this study.

References