Study methods extended

A nationwide dynamic cohort study was carried out in the Netherlands between April 1, 2012 and August 20, 2018 involving hospitals, nursing homes, rehabilitation centers and patients cared for at home. The inclusion criteria were as follows: (1) a diagnosis of VS/UWS in accordance with internationally accepted criteria, based on a standardized behavioral assessment using the Coma Recovery Scale-Revised (CRS-R) by a formally trained and experienced clinician[1]; (2) written, informed consent from the patient's representative; and (3) agreement on study participation by the treating physician.

The CRS-R, a behavioral observation assessment quantifying reactions to various sensory stimuli, communicative abilities and arousal, is considered the most sensitive and reliable scale to differentiate VS/UWS from MCS[2-4]. All CRS-R assessments in this study were carried out by the same researcher (WvE). Patients' families were invited to actively participate in the assessment. We recorded factors possibly interfering with the assessment, e.g. centrally acting medication, concurrent infections and time since previous administration of ANH[2, 5]. There were no exclusion criteria.

Patient recruitment was based on a nationwide VS/UWS prevalence study in the Netherlands in April 2012[6]. In order to identify new cases, the study was advertised in over 30 presentations to medical professional audiences, the distribution of flyers during symposia, and a website. The study protocol was evaluated by an accredited medical research ethics committee, which concluded that it did not meet criteria for medical scientific research according to the Dutch Medical Research Involving Human Subjects Act (1998). Additional ethical evaluation was therefore not indicated. All patients' representatives gave written informed consent. Follow-up was scheduled at 3-6-12 months after the causative incident and yearly thereafter. This meant that a patient included at 1 month post-ictus would receive 4 measurements within the first year while someone in VS/UWS included at 23 months post-ictus would be assessed once a year. Medical staff was explicitly asked to contact the researcher when the patient's reactions appeared to change between scheduled visits. Any suspected changes in consciousness that were reported to the study team would lead to an extra study visit.

Endpoints for follow-up were: recovery of signs of consciousness as detected with the CRS-R; end of study period, i.e. August 20, 2018; loss to follow-up, in case of repeated fruitless attempts at scheduling a new visit with the treating physician over telephone and e-mail (we aimed, in such cases, to ascertain whether the patient concerned was still in the care facility and thus, alive); or death.

At baseline and at each follow-up visit, the CRS-R was carried out and the treating physician was asked to fill in a questionnaire on the patient's clinical characteristics and treatment goals and limitations. Patients' trajectories through the healthcare system and aspects of the care they received were investigated at baseline as well. When an included patient died, the treating physician was asked to fill in a questionnaire on the cause of death, its circumstances and events and decisions preceding it. All posthumous data were verified with the treating physician over the phone, in order to prevent misinterpretation regarding treatment scenarios and causes of death as they prove to be difficult to catch in questionnaires[7]. Physicians were also invited to share any challenges, positive experiences or peculiarities they had encountered while caring for the included patient.

Data were stored in a secured and anonymized database. Statistical analyses were performed using SPSS 25.0. In order to minimize the influence of the variable times post-ictus at inclusion, inclusion bias and variable follow-up, outcome analyses were limited to the first two years post-ictus.

References

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Study results extended

A total of 59 patients possibly eligible for inclusion were clinically evaluated by the researcher. Twenty-eight out of 59 patients (47%) were found to be in a minimally conscious state (MCS). This resulted in a study population of 31 patients with a diagnosis of VS/UWS. See also table A.

Nineteen out of 31 patients (61%) were included within one year after the incident. At baseline, the average time post-ictus at inclusion was 3.5 years (SD 7 years, range 1 month – 33 years). Seventy – one percent of included patients had sustained non-traumatic brain injury (non-TBI), most often during an out-of-hospital cardiac arrest (OHCA) of cardiac origin (10/31 patients - 32% of the total group) (table 1). Over half of the population (52%) had a tracheostomy.

Of the 28 patients who had already been discharged from hospital at baseline, only one (4%) had followed specialized rehabilitation in a clinical rehabilitation center within the Netherlands. Six patients (21%) had received a correct level of consciousness diagnosis (either VS or UWS) at hospital discharge. The others conditions were described as 'poor neurological recovery', a Glasgow Coma Scale score or by stating the etiology (e.g. 'subarachnoid hemorrhage'). At nursing home admission, a diagnosis of VS/UWS or 'vegetative state' was made in 11 cases (39%). There was no mentioning of CRS-R scores accompanying any of the hospital or nursing home diagnoses.

The treating physician was an elderly care physician in 18/31 cases (58%), a resident or junior doctor in ten (32%), a neurologist in three cases and a general practitioner in one case.

Patients less than 1 year post-ictus received a median of 2 measurements (range 2-5) within a median follow-up duration of 6 months (range 1 month – 3 years 8 months). Patients in VS/UWS for over a year received a median of 3 measurements (range 2-7) and were followed for a median duration of 2 years (range 3 months – 6 years). Time between measurements never exceeded 10 months.

Twenty-three percent of follow-up and posthumous questionnaires remained unanswered. All but one CRS-R assessment were completed as scheduled according to protocol. Relatives participated in 71% of CRS-R assessments. Possible interference was at hand in 59% of assessments due to medication with known centrally acting and potentially sedative side-effects, in 22% due to low arousal (wakefulness score on CRS-R of 0 or 1), in 19% due to somatic disturbances such as concurrent infections or seizures in the previous days, and in 54% of measurements the last administration of ANH had been less than an hour before, or the patient received continuous ANH. In 9% of CRS-R assessments, no factors possibly negatively influencing performance were present.

Outcome data are as follows. Out of the 22 non-TBI patients, eight (36%) died within two years post-ictus and three (14%) emerged to MCS without command following (figure A). Of the nine traumatic VS/UWS patients, four (44%) died, one emerged to MCS without command following and one recovered consciousness within two years post-ictus (figure B). During the total course of the study, six patients emerged from VS/UWS. Three patients were alive in VS/UWS when the study ended. Four patients, all confirmed to be alive when the study ended, were lost to follow-up because of non-respondent physicians.

Eighteen out of 31 patients died during the course of the study. Eleven of them did so within 2 years post-ictus; the others died between 4 and 33 years post-ictus. Mean age at death was 50 (SD 12 years, range 26-67 years). Scenarios of dying are listed in table 1 in the main manuscript. Three patients were unexpectedly found deceased: one presumably due to an epileptic seizure causing hypoxemia, while the causes of death in the other two remained unclear, even after autopsy in one. One patient died due to sudden respiratory failure despite curative treatment. Two died after a decision not to treat a new, life-threatening complication (e.g. pneumonia). Nine out of 18 deaths (50%) occurred after withdrawal of ANH.

All physicians in charge of these nine cases were elderly care physicians, four of whom had expressed the intention to withdraw ANH in this case earlier in the study. Based on the questionnaires (n=9) and telephone verification (n=7), every decision to withdraw ANH was tied to a specific event or development. This 'trigger' was a somatic complication such as an infection in five cases. An factor unrelated to the patient's clinical condition led to the decision in the other four. Two arose from the research itself (e.g. repeated confirmation of the diagnosis by an expert not affiliated with the patients care institution). In the other two, a dysfunctional feeding tube led to ANH being withdrawn. Most physicians (6/9) considered themselves responsible for this decision; the other three felt they shared responsibility with the patient's relatives. According to the physicians, none of the decisions were made without the relatives' consent.

Detailed information on the patient's last days was obtained in seven cases. After discontinuation of ANH, all patients were, either pro-actively or reactively, treated with midazolam and morphine to alleviate signs of possible discomfort. Anti-epileptic drugs were abruptly stopped in the three patients who had been receiving them; two of them developed seizures. The time span between withdrawal of ANH and death varied. Two patients, both with severe complications and co-morbidity (ileus, diabetes mellitus type 1), died within 48 hours. Four others survived for over a week, one somatically healthy man in his forties even for 18 days. In three of these cases lasting for over a week, treating physicians mentioned unprompted that they had felt the 'emaciation' (physicians' quotes) that occurred after ANH was discontinued to have compromised the 'patient's dignity' (physicians' quotes). Two physicians spontaneously reported being asked by family members 'to euthanize the patient' (physicians' quotes). In accordance to the strict euthanasia regulations in place in the Netherlands, these requests were not granted[1].

References

1. Royal Dutch Medical Association. The role of the physician in the voluntary termination of life. KNMG. 2011.

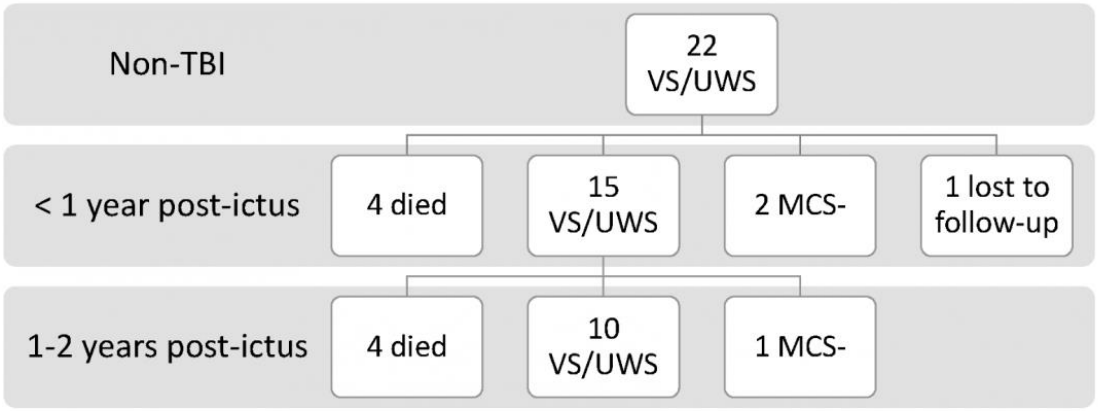
Table 1. Demographics, clinical characteristics and health care aspects of patients in VS/UWS (n=31)

Sex (F/M)	16/15	
Mean age at inclusion (years, months)	45y6m (SD 14y, range 17-68y)	
Marital status	Married or (registered) partnership	20 (65%)
	No relationship	11 (35%)
Patient's representative	Partner	16 (52%)
	Parent	8 (26%)
	Child	4 (12%)
	Other	3 (10%)
Mean age at incident (years, months)	42y 1m (SD 16y, range 14-65y)	
Mean time post-ictus (years, months)	3y 5m (SD 7y, range 1m – 33y)	
Etiology	Non-trauma	22 (71%)

	- OHCA	12 (10 cardiac cause)
	- SAH	3
	- Surgical complications	3
	- Miscellaneous non-trauma	4
	Trauma	9 (29%)
	- Traffic accident	6 (4 car, 2 bicycle)
	- Fall	2
	- Sports injury	1
Invasive devices	Tracheostomy	16 (52%)
	- Cuffed	8
	- Uncuffed	8
	Artificial nutrition and hydration	31 (100%)
	- Nasogastric tube	5
	- PEG	24
	- PEG – jejunal	2
	Urinary catheter 16/31	16 (52%)
Location at inclusion	Nursing home	26 (84%)
	Neurology ward in hospital	3
	Transfer unit in hospital	1
	At home	1
Treating physician	Elderly care physician	18 (58%)
	Resident	6
	Junior doctor	4
	Neurologist	2
	General practitioner	1
Rehabilitation	No rehabilitation	20
	Specialized rehabilitation in clinical rehabilitation centre	4 (3 abroad)
	Specialized rehabilitation in nursing home	4
	Does not apply, patient still in hospital	3
Diagnosis at hospital discharge, according to discharge documentation	10 formal level of consciousness diagnosis (2 'comatose', 1 'subcomatose', 1 'coma vigil', 5 'vegetative state', 1 UWS) 5 GCS score 3 'poor/ no neurological recovery' 7 etiologic description 4 missing 2 does not apply, patient still in primary hospital	
Diagnosis at admission in long-term care, according to medical records	18 formal level of consciousness diagnosis (4 'comatose', 2 'coma vigil', 1 'unconscious', 6 'vegetative state', 5 UWS) 2 GCS score 4 no diagnosis 5 missing 2 does not apply, patients still in primary hospital	

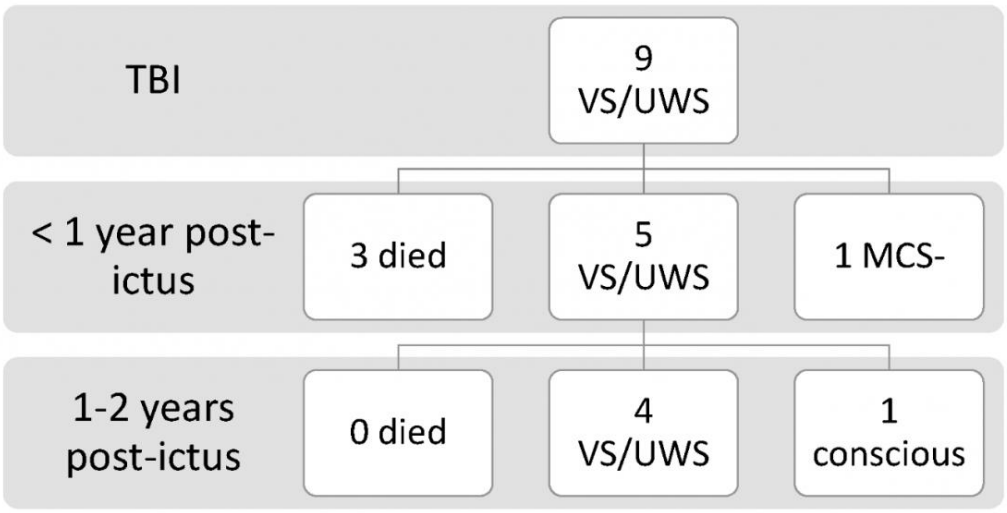
Legend: OHCA, out-of-hospital cardiac arrest; SAH, subarachnoid hemorrhage; PEG, percutaneous endoscopic gastrostomy; GCS, Glasgow Coma Scale.

Figure A



Outcomes in VS/UWS patients with non-traumatic brain injury (non-TBI)

Figure B



Outcomes in VS/UWS patients with traumatic brain injury (TBI)