



THE UNRESPONSIVE WAKEFULNESS SYNDROME IN THE NETHERLANDS: OUTCOMES FROM A VICIOUS CIRCLE

WILLEMIJN VAN ERP

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Willemijn van Erp



COLOFON

Cover Hoogstede Ontwerpt, 2020
Design Hoogstede Ontwerpt
Print Libertas Pascal. This thesis was printed on 100% recycled, FSC-certified paper.

Funding

All research described in this thesis was funded by the Stichting Beroepsopleiding Huisartsen (SBOH), with additional support from Universitair Kennisnetwerk Ouderenzorg Nijmegen (UKON), and from My-doc. Printing expenses were kindly reimbursed by SBOH and Radboudumc.



Radboud University

The work presented in this thesis was carried out within the Radboud Institute for Health Sciences.
An electronic version of this thesis is available at <https://hdl.handle.net/2066/220229> and
<https://www.ukonnetwerk.nl/publicaties/willemijn-van-erp/>

ISBN 9789464023992

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PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Radboud Universiteit Nijmegen op
gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken, volgens besluit van het
college van decanen

en

ter verkrijging van de graad van doctor aan de Universiteit van Luik op gezag van de rector
magnificus prof. dr. P. Wolper

in het openbaar te verdedigen op woensdag 4 november 2020 om 16.30 uur precies

door Willemijn Sabien van Erp

geboren op 8 augustus 1985 te Nijmegen



Promotoren

Prof. dr. Raymond Koopmans

Prof. dr. Steven Laureys (Universiteit van Luik, België)

Copromotoren

Dr. Jan Lavrijsen

Dr. Pieter Vos (Slingeland Ziekenhuis)

Manuscriptcommissie

Prof. dr. Karin Klijn

Dr. Astrid Hoedemaekers

Prof. dr. Hans van Delden (Universitair Medisch Centrum Utrecht)



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DOCTORAL THESIS

to obtain the degree of doctor from Radboud University Nijmegen

on the authority of the rector magnificus prof. dr. J.H.J.M. van Krieken, according to the
decision of the council of deans

and

to obtain the degree of doctor from University of Liège

on the authority of the rector magnificus prof. dr. P. Wolper

to be defended in public on Wednesday, November 4, 2020 at 16.30 hours

by Willemijn Sabien van Erp

born August 8, 1985 in Nijmegen (the Netherlands)



Supervisors

Prof. dr. Raymond Koopmans

Prof. dr. Steven Laureys (University of Liège, Belgium)

Co-supervisors

Dr. Jan Lavrijsen

Dr. Pieter Vos (Slingeland Hospital)

Doctoral thesis committee

Prof. dr. Karin Klijn

Dr. Astrid Hoedemaekers

Prof. dr. Hans van Delden (University Medical Center Utrecht)



**Le syndrome d'éveil non répondant aux Pays-Bas:
les solutions d'un cercle vicieux**

THÈSE

présentée en vue de l'obtention du grade de docteur de l'Université Radboud de Nimègue
sous l'autorité du recteur magnificus prof. dr. J.H.J.M. van Krieken, selon la décision du
conseil des doyens

et

en vue de l'obtention du grade de docteur de l'Université de Liège sous l'autorité du
recteur magnificus prof. dr. P. Wolper

a défendre publiquement le mercredi 4 novembre 2020 à 16h30 exactement

par Willemijn Sabien van Erp

née le 8 août 1985 à Nimègue (les Pays-Bas)

**Promoteurs**

Prof. dr. Raymond Koopmans

Prof. dr. Steven Laureys (Université de Liège, la Belgique)

Co-promoteurs

Dr. Jan Lavrijsen

Dr. Pieter Vos (Slingeland Hospital)

Comité de thèse de doctorat

Prof. dr. Karin Klijn

Dr. Astrid Hoedemaekers

Prof. dr. Hans van Delden (University Medical Center Utrecht)



Note

This thesis discusses the unresponsive wakefulness syndrome, a clinical condition previously called ‘the vegetative state’. As the term ‘vegetative’ tends to raise disrespectful associations with plants and vegetables, and ‘state’ implies a stationary character incongruent with the fact that many patients eventually regain (minimal) awareness, me and my co-authors prefer to use the new name, i.e. unresponsive wakefulness syndrome. However, to this day some international journals and reviewers require the use of ‘vegetative state’ in publications. This explains why in some chapters in this manuscript one term is used, in some the other, and in some both. Both terms refer to the same diagnostic entity.



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1

INTRODUCTION



The primary goal of medicine has classically been to prolong life. Over the last century, chances of survival for the severest injuries and diseases have dramatically increased⁽¹⁾.²⁾ The notion that the yield of this progress was not exclusively positive started to emerge early in the 1950s. Having overcome the critical first hours to days after acute brain damage, incidentally patients remained in a state devoid of ‘evidence suggesting them to be in touch with their surroundings’⁽³⁾. The general public in the Netherlands first learned about such outcomes in 1966, when the father of a young woman called Mia Versluis sought public attention. She had permanently lost consciousness due to hypoxemia during an elective surgical procedure⁽⁴⁾.

In 1972, British neurosurgeon Bryan Jennett and American neurologist Fred Plum proposed the term ‘persistent vegetative state’, to describe a condition of autonomous vital functions and spontaneous eye opening without evidence of conscious awareness⁽⁵⁾. It had previously been known as ‘coma vigil’ and ‘apallic syndrome’. In years to follow, ‘vegetative’ patients following acute, acquired brain injury increasingly became the subject of neuroscientific, clinical and public attention. These three perspectives crossed regularly, but were not as intertwined as might have been beneficial to the patients, families and health care professionals involved.

***Disorders of consciousness in science and society:
is anybody in/ out there?***

Science took on a quest to find out what went on in the minds of people with prolonged disorders of consciousness (PDOC). In the early 2000s a subpopulation of hyporesponsive patients was found to retain some, albeit minimal, awareness of themselves and their surroundings⁽⁶⁾. This condition was eventually coined ‘minimally conscious state’ (MCS), and corresponded to better chances of further recovery⁽⁷⁾ and the ability of sensory processing, including nociception⁽⁸⁾. But even for patients without behavioral signs of consciousness, the botany-associated, motionless term ‘vegetative state’ became less and less appropriate. In 2010, a new name was proposed: the unresponsive wakefulness syndrome (UWS)⁽⁹⁾. Novel, sensitive imaging techniques



such as fMRI gradually became accepted methods to detect brain activity deemed ‘too complex’ *not* to reflect awareness⁽¹⁰⁾. A gold standard for level of consciousness determination, however, is yet to be developed⁽⁷⁾ as are ways to restore and sustain full conscious awareness and communication in UWS and MCS patients.

Meanwhile in daily practice, physicians in charge of PDOC patients carry a tremendous responsibility. Especially in long-term care, these patients stand out: they are younger than the average nursing home population but require most intensive care and treatment. The public image of disorders of consciousness has been romanticized, with movie characters regularly falling into ‘coma’ and re-emerging again in an even better version of themselves⁽¹¹⁾. To those providing care to actual patients in UWS and MCS, however, it has always been clear that such Sleeping Beauty scenarios could not be further from reality^(11a).

Much of what is known about that reality arises from long-term care research. Specifically in the Netherlands, publications about the diagnosis, natural course and complications of UWS have explicitly discussed the ethical implications of the topics at hand as well.

In 1990, a Dutch case report presented the withdrawal of artificial nutrition and hydration (ANH) in a patient who had been in UWS for 6.5 years⁽¹²⁾. The fact that in the Netherlands end-of-life decisions in UWS are made by treating physicians without involvement of the court is a direct result of this publication. It came at the height of a public debate about the justifiability of life-prolonging treatment and of its cessation in prolonged UWS. In preceding years, Gerard Stinissen had argued for his wife Ineke to be allowed to die after complications during a cesarean section had left her unresponsive⁽¹³⁾. His eloquent, passionate, and sometimes militant appeal to health care professionals, politics and the justice system led to the withdrawal of ANH in his wife’s case in 1990. The aforementioned elderly care physician’s report of another young female UWS patient, and of the decision – after extensive deliberation with her family, medical staff and ethicists – to discontinue her life-prolonging treatment, ultimately brought the process



of medical decision-making back from the courtroom to the clinic⁽¹⁴⁾. Subsequent reports by the Health Council (1994) and the Royal Dutch Medical Association (1997), stated, respectively, that the discontinuation of artificial nutrition and hydration in unresponsive patients without chances of recovery of consciousness was justifiable, and that the *continuation* of ANH in such cases was not^(15, 16).

While these texts clarified the Dutch limits to life-prolonging treatment for UWS, optimal therapy in itself would remain inaccessible for the majority of affected individuals for over 2 decades. In 1986, a young girl with PDOC after traumatic brain injury was the first patient to receive specialized rehabilitation in the Netherlands⁽¹⁷⁾. This program was gradually extended and professionalized, but only for PDOC patients up to the age of 25⁽¹⁸⁾. Specialized treatment for ‘older’ UWS and MCS patients would not be reimbursed until 2019; formally, it was not even considered rehabilitation.

This high threshold for early, intensive neurorehabilitation existed next to an increasingly academically professionalized long-term care, staffed by formally trained elderly care physicians^(19, 20). Over the years nursing homes all over the Netherlands developed dedicated rehabilitation and long-term care for UWS and MCS patients, in spite of the absence of proper financial and logistic facilitation. Some of the elderly care physicians providing this care also produced the first scientific insights into the size of the Dutch UWS population, the complications that occurred, and the way these patients lived and died.

Long-term care research on UWS: what we do and do not know

In 2003, 32 patients with the diagnosis ‘vegetative state’ were identified in Dutch nursing homes, with ages ranging from 9 to 90 years old and stroke being the most frequent etiology. Three of these patients (9%) had their diagnosis verified by the researchers⁽²¹⁾. Another group of 76 patients with the same diagnosis was retrospectively found to have been admitted between 2000 and 2003 to long-term care facilities⁽²¹⁾. Twenty of



them were reported to have recovered on discharge, 43 died. In following years, a rare ophthalmic condition and severe osteoporosis were recognized as specific complications of prolonged UWS^(22,23). Qualitative insights into end-of-life decision-making arose from a 2005 retrospective case series of five patients in UWS for over 12 months⁽²⁴⁾. Four different scenarios regarding life-prolonging treatment were identified in relation to complications, intensive medical and paramedical care and the various standpoints of the families and physicians involved. The scenario of ANH withdrawal, as identified in this publication, appeared to be relatively rare in the early 2000s. Within the aforementioned retrospective cohort of 76 UWS patients, it had occurred prior to 9/43 deaths. Death after a decision not to treat complications was more prevalent, accounting for 24/43 cases⁽²⁴⁾.

Since these publications, much knowledge has been gained about UWS, particularly about its neurophysiologic substrate⁽²⁵⁾. Nonetheless, the 2018 guidelines on disorders of consciousness by the American Academy of Neurology highlight that the evidence with regard to the natural history of UWS is still 'limited'⁽⁷⁾. There remains a need for reliable and actual prevalence figures and for prospective studies on the course of UWS and MCS. The commonly used prognostic timeframes in which recovery of consciousness is to be expected, i.e. 3–6 months after non-traumatic or 12 months after traumatic brain injury^(15,26,27), appear to be too pessimistic⁽⁷⁾. In addition, clinicians and researchers have become cautious of clinical consensus diagnoses in UWS. Despite the widely recognized clinical importance of an accurate distinction between UWS and MCS, in 41% of patients signs of consciousness go undetected or are misinterpreted⁽²⁸⁾. This risk of misdiagnosis compromises the interpretability and translatability of many preceding papers, especially those based on retrospective research and predating the definition of MCS in 2002⁽⁶⁾.

Diagnostic accuracy and reliable facts about the long-term course of UWS, including the end of life, can also be considered a prerequisite for ethical considerations. The debate on how patients with disorders of consciousness should be treated and who gets to decide about that treatment, is ongoing throughout the world. These discussions would benefit



from factual input, especially from a country that took a stand on this topic over 20 years ago. All in all, Dutch long-term care provides a unique context for UWS research and a possible source of scientific data with a high societal impact, perhaps even on a global scale.

This thesis and its purpose

In 2011, I was selected for one of the first combined trajectories of a specialization in elderly care medicine and a PhD project. Being trained in research and clinical practice simultaneously allowed for continuous interaction between both worlds. During internships in various health care settings dedicated to patients with the severest outcomes of acquired brain injury, the need for better understanding of some of the worst conditions in modern medicine never left my attention.

With this thesis, I hope to make a contribution to that understanding. I will present the situation of UWS patients as it is in the somewhat atypical Dutch context and relate it to international scientific perspectives. How many people are in UWS, according to the existing international literature? What is the prevalence of UWS in the Netherlands, with its limited access to specialized post-acute care and specific view on life-prolonging treatment once chances of recovery have passed? How do UWS patients fare beyond the first month of their injury? Do they recover, how do they survive, and if they die, how does that happen? And what can be learned from all these observations, in the pursuit of the tailor-made care UWS patients and their families deserve?

Thesis outline

In chapter 2, UWS prevalence studies are systematically reviewed.

Chapter 3 describes a nationwide prevalence study on UWS. It was carried out in 2012 and involved all hospitals, rehabilitation centers and nursing homes in the Netherlands.



Patients with a clinical consensus diagnosis of VS/UWS were assessed using the Coma Recovery Scale- Revised (CRS-R)⁽²⁹⁾, the behavioral scale considered the most sensitive and reliable in distinguishing MCS from UWS^(7,30), before being included and we gathered various clinical and care-related characteristics.

In chapter 4, the Dutch perspectives on UWS are discussed, comparing the results of the 2012 prevalence study to historical data arising from the same context.

Chapter 5 presents the stories of UWS patients as they unfolded over the years, as observed during a dynamic cohort study. The evolution of patients' level of consciousness, the care they did and did not receive, their survival and end of life are discussed. These data are then related to the way healthcare for UWS and MCS has classically been organized in the Netherlands specifically, and to end-of-life decision making for these patients in general.

Chapter 6 unravels the cases of four UWS patients who were found to have recovered consciousness unexpectedly late during the cohort study. Based on extensive analysis of their clinical files and of the patients' families' accounts, we reconstructed the moment signs of consciousness first appeared. This leads to the question whether these were cases of late recovery of consciousness, or of late discovery.

The results of this thesis, and the implications of the findings for clinical practice, competence development of health care professionals and future research, are discussed in chapter 7.



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2

THE VEGETATIVE STATE/ UNRESPONSIVE WAKEFULNESS SYNDROME: A SYSTEMATIC REVIEW OF PREVALENCE STUDIES

Willemijn S. van Erp • Jan C.M. Lavrijsen • Floris A. van de Laar • Pieter E. Vos •
Steven Laureys • Raymond T.C.M. Koopmans • European Journal of Neurology 2014; 21(11): 1361-1368



ABSTRACT

One of the worst outcomes of acquired brain injury is the vegetative state, recently renamed ‘unresponsive wakefulness syndrome’ (VS/UWS). A patient in VS/UWS shows reflexive behaviour such as spontaneous eye opening and breathing, but no signs of awareness of the self or the environment. We performed a systematic review of VS/UWS prevalence studies and assessed their reliability. Medline, Embase, the Cochrane Library, CINAHL and PsycINFO were searched in April 2013 for cross-sectional point or period prevalence studies explicitly stating the prevalence of VS/UWS due to acute causes within the general population. We additionally checked bibliographies and consulted experts in the field to obtain ‘grey data’ like government reports. Relevant publications underwent quality assessment and data-extraction. We retrieved 1032 papers out of which 14 met the inclusion criteria. Prevalence figures varied from 0,2 – 6,1 VS/UWS patients per 100 000 members of the population. However, the publications’ methodological quality differed substantially, in particular with regards to inclusion criteria and diagnosis verification. The reliability of VS/UWS prevalence figures is poor. Methodological flaws in available prevalence studies, the fact that 5/14 of the studies predate the identification of the minimally conscious state (MCS) as a distinct entity in 2002, and insufficient verification of included cases may lead to both overestimation and underestimation of the actual number of patients in VS/UWS.



INTRODUCTION

For patients surviving severe brain damage of either traumatic or non-traumatic origin, one of the worst possible outcome is the vegetative state, recently renamed ‘unresponsive wakefulness syndrome’ (VS/UWS)^[1]. A patient in VS/UWS shows reflexive behaviour such as spontaneous eye opening and breathing, but no signs of awareness of the self or the environment^[2,3].

While science is steadily unravelling the physiological basis of disorders of consciousness^[4], the number of patients in VS/UWS remains unclear; the most commonly cited prevalence figures are based on estimates^[5,6]. This is partly due to diagnostic difficulties, reflected in a high misdiagnosis rate: up to 43% of patients presumed to be in VS/UWS turn out to be at least in a minimally conscious state (MCS)^[7] when examined by means of a structured assessment scale^[8,9]. The difference between MCS and VS/UWS is of considerable clinical relevance: patients in MCS appear to have a better prognosis^[10-12] and to process emotional, auditory and noxious stimuli in a way very similar to that of healthy individuals^[13,14].

Epidemiological data form the basis of insight in every clinical condition. In order to apprehend the impact of a disease or syndrome, the number of patients it affects is one of the first things clinicians, scientists and policy makers need to know. The prevalence of VS/UWS, a condition often referred to as ‘a fate worse than death’^[15], is therefore relevant to epidemiologists, neurologists, primary care physicians, physiatrists, ethicists and policy makers. This paper gives an extensive overview of VS/UWS prevalence figures and their reliability by means of a systematic review.

METHODS

A literature search of Medline, Embase, the Cochrane Library, CINAHL and PsycINFO was carried out in April 2013, using complete timescales and no language restrictions or other limits. We used the following search terms: ‘vegetative state’, ‘unresponsive



wakefulness syndrome', 'apallic syndrome' and 'akinetic mutism', combined with search terms for epidemiology (appendix 1). Experts in the field were asked for so-called grey data, e.g. governmental reports or personal communications possibly containing VS/UWS prevalence figures.

Titles and abstracts were scanned for relevance by two researchers (WvE, JL) independently. Whenever at least one of the researchers considered a paper relevant or possibly relevant, it was read full text. Publications were included provided they were original cross-sectional point or period prevalence studies, explicitly stating the number of VS/UWS patients within the general population. We excluded studies that concerned only VS/UWS due to degenerative and other non-acute causes, outcome studies within populations with specific medical characteristics (e.g. out-of-hospital cardiac arrest, subarachnoid hemorrhage), and papers post-dating 1994 not using the Multi-Society Task Force on PVS-criteria^[3]. The latter criterion, however, was dropped as it soon turned out to exclude nearly all otherwise eligible publications.

Upon inclusion, both researchers independently assessed study quality in a structured manner (appendix 2), based on an earlier systematic review of prevalence studies^[16] and two methodological papers^[17,18]. In short, we looked at study design, whether a point or period prevalence was obtained, response rates in case of questionnaires, the way estimates were constructed and the manner of diagnosis verification in included cases. Although no gold standard for the diagnosis of VS/UWS exists, expert opinions agree on the fact that a validated assessment tool for the level of consciousness after the acute phase should be used, preferably the Coma Recovery Scale- revised^[19-21]. Repeated assessments and the involvement of proxies and professionals familiar with the patient are recommended^[22-24]. Complementary diagnostics like fMRI and EEG could be considered as well^[24,25]. Next to these items, we checked whether authors mentioned the presence of consensus about the diagnosis in included cases.

When needed in the process of quality assessment, agreement was reached through discussion. As one researcher (JL) was the author of one of the publications^[26], a third,



independent researcher (FvL) carried out quality assessment in this case. We recalculated absolute patient numbers to prevalence per 100 000 people if demographic data from the period concerned were available on www.oecd.org.

RESULTS

The search strategy and consultation of three experts in the field produced 1001 unique records. Of every publication considered relevant or possibly relevant by one or both authors ($n=107$), including 31 additional titles from bibliographies, full text was evaluated for eligibility. In 4 out of 107 cases we were unable to obtain the original publication^[27-30], despite attempts to contact the authors. A further 89 papers were discarded as their full texts did not meet inclusion criteria. Finally, 14 studies were included. A flow chart of the selection procedure is shown in figure A and study characteristics can be found in table 1.

Figure A. Study selection, reported in agreement with the PRISMA statement^[31].

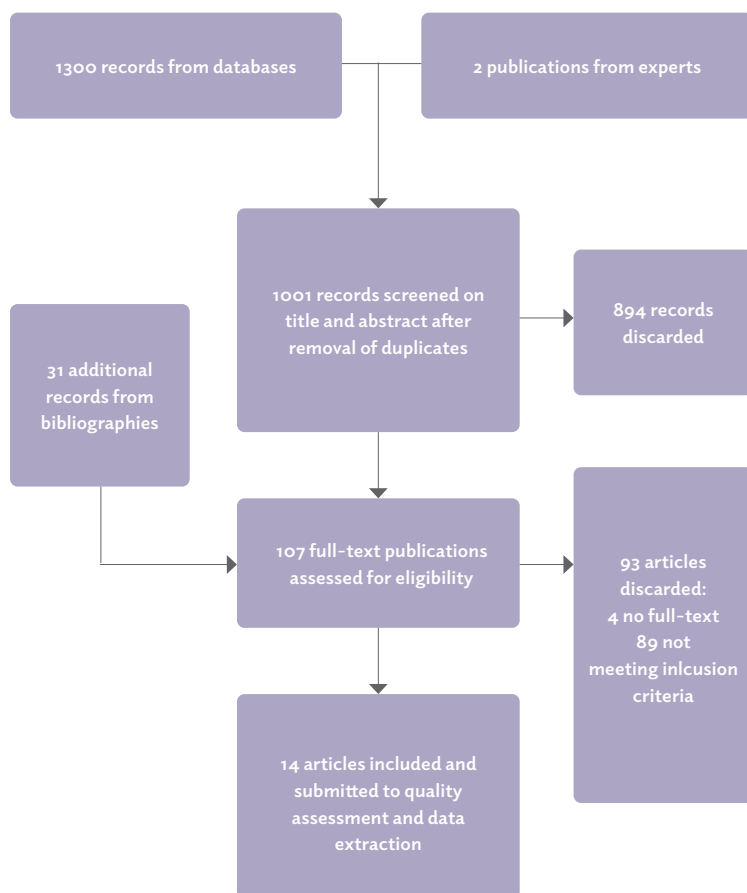






Table 1. Characteristics of studies included (*italic figures calculated by authors*)

First author, year of publication	Study year	Population	Diagnostic criteria; Inclusion of degen. causes	Point/ period prevalence; Method
1. [32] Kodama (1976)	1972	All neurosurgical clinics in Japan	Local criteria; Degen. causes included	Unclear; Questionnaire to clinics
2. [33] Higashi (1977)	1973	All hospitals in Yamaguchi (Japanese prefecture)	Local criteria; Degen. causes included	Point; Questionnaire to hospitals
3. [34] Sato (1978)	Unclear (<1978)	All hospitals with registered VS/ UWS pts in Tohoku (Japanese district)	Local criteria; Degen. causes included	Unclear; Pts identified through insurance system, then questionnaire to hospitals
4. [35] Minderhoud (1985)	1983	Hospitals, nursing homes, Netherlands (unclear whether nationwide or regional)	Unclear; Only acute causes	Unclear; Questionnaire to hospitals and nursing homes
5. [36] Tasseau (1991)	1987	Unclear; 18/23 regions in France	Unclear; Unclear	Unclear; Unclear
6. [37] Ashwal (1992)	1991	Patient populations of Child Neurology Society-members, USA	Unclear; definition was subject to discussion within the questionnaire	Unclear; Questionnaire sent to all members of CNS (presumably covering the country)
7. [38] Engberg (2004)	1997	Brain injury registry, 4 Danish regions	Unclear; traumatic causes, surviving > 5 years after injury	Point; From the outcomes of patients with TBI in 1982, 1987 and 1992 the prevalence of VS/ UWS is calculated



Response rate	Validation	Result	Remarks
90% of clinics	None	646 (abs) 'approx. 2000 in Japan' 0.6/100,000	Inclusion criteria cover MCS
Unclear	100%; unvalidated assessment by researcher within unknown timeframe	2.5/100,000	Inclusion criteria cover MCS; Terms 'prevalence' and 'incidence' used erroneously
78%	None	1.88/100,000 Authors estimate actual prevalence to be 2-3/100,000	Inclusion criteria cover MCS; Terms 'prevalence' and 'incidence' used erroneously
79,6%	None	53 (abs) 0.37/100,000	
Unclear	Unclear	2.0/100,000 ('all VS patients') 1.4/100,000 ('patients in VS > 3 months')	Personal communication cited in book, limited information
250/960 26%	None	1600 children (abs), extrapolated to 6000 (abs) 0.63/100,000	Extrapolation. Authors hypothesize that the actual number may be higher.
Does not apply	None	<0.13/100,000 (figure follows from the fact that sample contained no VS/UWS)	Possibility of sampling error not discussed Terms 'prevalence' and 'incidence' used erroneously



8. [39] Plexus Medical Group (1998)	1997	Sample, no information except indirectly; 2 academic hospitals, 10 general hospitals, 18 nursing homes in 6 cities in the Netherlands	'Coma patients', GCS < 7, > 4 weeks; Unclear	Period; Questionnaire to hospitals and nursing homes
9. [40] Stepan (2004)	2001	All hospitals and nursing homes in Vienna, Austria	Local criteria, patients in VS/UWS > 14 days; Unclear	Point; Inventory of potential cases 1 month before study date, then validation
10. [26] Lavrijsen (2005)	2003	All nursing homes in the Netherlands	[3], > 1 month after acute injury	Unclear; Announcement with diagnostic criteria, then interview by phone with all institutions
11. [41] Stepan (2006)	2003	All hospitals and nursing homes in Vienna, Austria	Local criteria, patients in VS/UWS > 14 days; Unclear	Point; Inventory of potential cases 1 month before study date, then validation of reported cases
12. [42] Saoût (2010)	Unclear (<2010)	All nursing homes, hospitals and rehabilitation centres in Maine-et-Loire county, France	Unclear; Unclear	Unclear; Questionnaire to all institutions
13. [43] Pistarini (2010)	2002-6	All hospitals, Italy	Unclear; Unclear	Unclear; National registry of hospital discharge diagnoses checked for VS/UWS
14. [44] Donis (2011)	2007-9	All nursing homes, Austria	[3]; Unclear	Period; Inventory of potential cases, then interview by phone for reported cases



29/30	None	1.045/ 100.000	National prevalence calculated as the mean of city prevalence figures
96,7%			Possibility of sampling error not discussed

96%	88%; assessment by researcher within 3 days after study date; Glasgow coma scale, Glasgow outcome scale, Edinburgh 2 coma scale, Barthel score	1.9/ 100,000	1 patient excluded for not being from the region
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100%	3/32 9.4%; WNSSP	0.2/ 100,000	Validation only when doubt about diagnosis 11. [41] Stepan (2006)
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98%	100%; assessment by researcher within 3 days after study date; Glasgow coma scale, Glasgow outcome scale	1.7/ 100,000	1 patient excluded for not being from the region
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Unclear	100%; assessment by researcher within unknown timeframe, WHIM	2.8/ 100,000 4 VS/UWS + 9 MCS 0,86/ 100,000	No prevalence given for VS/ UWS separately
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Does not apply	None	6.1/ 100,000 'crude estimate', possibly a mean value for all years.	Only calculated for Lombardia region. Conference abstract, limited information
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100%	None	3.36/ 100,000	
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Over the past 40 years, 14 prevalence studies on VS/UWS were found to have been published, originating from Japan, the Netherlands, France, the USA, Denmark, Austria and Italy. The average year of publication was 1996 (range 1976–2011). We will discuss the studies' methodological characteristics and the prevalence figures they led to.

Researchers used various strategies to identify patients, varying from questionnaires to the members of the Child Neurology Society^[37] to insurance registries^[34] and phone interviews with nursing homes' medical directors^[26]. In prevalence studies based on questionnaires, response rates turned out fairly high (78–100%) with the exception of a 26% response in a survey amongst members of the Child Neurology Society^[37]. Information about non-responders was lacking in all cases. Three papers based on surveys did not mention response rates^[33,36,42]. Sampling frames (i.e. the populations in which the prevalence was investigated) were countries or smaller geographical regions. It should be noted that 2 papers based their prevalence on the nursing home population exclusively^[26,44], and that none of the studies included patients being cared for at home. Demographic and socioeconomic variables possibly affecting the samples were described in none of the studies. The 2 papers in which results from a smaller sample were extrapolated to a nationwide prevalence figure gave no indication of corrections for sample bias^[38,39]. Estimates in these and other studies came without confidence intervals^[32,34,37–39,43].

Eight studies^[26,38,40–43,45,46] were carried out after the publication of internationally accepted diagnostic criteria for VS/UWS^[3]; 3 of them also used these as their inclusion criteria^[26,44,47]. Nine prevalence studies^[32,36,38,40,45,48–51] took place before the identification of the minimally conscious state (MCS) as a distinct entity in 2002^[7] and 3 of these publications explicitly stated inclusion criteria which also cover MCS (e.g. visual fixation, inconsistent command following)^[32,48,49]. Diagnoses of included patients were verified by researchers in 5/14 studies^[26,33,40–42]. Two groups^[26,42] deployed scales specifically designed for level of consciousness determination in the post-acute setting: the Western Neuro Sensory Stimulation Profile^[52] and the Wessex Head Injury Matrix^[53], respectively. In the remaining 3 studies^[33,40,41], researchers used unvalidated assessment methods, descriptive



scales (e.g. the Glasgow Outcome Scale^[54]) and/or scales unsuitable for level of consciousness assessment in the post-acute and long-term setting, such as the Glasgow Coma Scale^[55]. Case verification was carried out within 3 days in 2 studies^[40,41], while the time lapse between study date and assessment remained unclear in the other 3. One study involved caregivers' and/or proxies' observations and whether consensus about the patient's diagnosis existed between those two parties, but only verified cases in which there were doubts about the diagnosis^[26]. In none of the studies, repeated assessments or complementary diagnostics, such as functional magnetic resonance imaging, seem to have been used.

Four papers discussed point prevalence^[33,38,40,41] and 2 studies reported period prevalence figures^[45,46]. From 8/14 studies, it remained unclear whether a point or a period prevalence had been the objective^[26,32,35,37,39,42,43,56]. The terms 'prevalence' and 'incidence' were used erroneously in 3 papers^[33,34,38]. As the number of patients at a certain time point was clearly mentioned in these texts, we remained able to extract the prevalence figures.

Keeping aforementioned methodological differences in mind, the prevalence figures showed a broad variety from publication to publication. Authors of one study concluded that the prevalence in their population had to be less than 0.13/100 000 as there were no VS/UWS patients in a sample of 389 individuals^[38]. This figure set aside because of the small sample it arose from, according to literature the prevalence of VS/UWS varies from 0.2/100 000 (the Netherlands, 2003)^[26] to 6.1/100 000 inhabitants (Lombardia, Italy 2009–10)^[43].

DISCUSSION

This systematic review of prevalence studies on VS/UWS shows a wide range in available prevalence figures, from 0.2/100 000 to 6.1/100 000 inhabitants^[26,43]. Interestingly, no publications were found from the African continent, Latin-America or Asia outside of Japan, while this last country accounted for 3/14 of the publications (as did Austria and



the Netherlands). The broad distribution of VS/UWS prevalence figures themselves may be attributable to various factors.

First of all, the prevalence of VS/UWS is expected to vary between and maybe even within countries due to quality and availability of emergency and intensive care services^[58]. Secondly, end-of-life decisions in the intensive care unit, on hospital wards, and in post-acute and long-term care settings are strongly influenced by a country's political, professional, judicial and cultural profile^[59]. The Netherlands, for example, allows for withholding life-sustaining medical treatment and withdrawal of artificial nutrition and hydration (ANH) in VS/UWS once prognostic boundaries of recovery of consciousness have passed^[60,61]. Between 2000 and 2003, 9 out of 43 deaths of VS/UWS patients were preceded by cessation of ANH and 24 by a decision not to treat complications^[26]. The low Dutch VS/UWS prevalence, 30 times smaller than what was found in the Italian study, might be partially attributable to this.

However, we believe that the considerable different ways in which the prevalence studies were carried out render it impossible to draw legitimate conclusions on this sensitive subject. This brings us to a third explanation of the differences in VS/UWS prevalence. What the assessment of the included studies' methodological quality reflects, is the challenge of shedding light on a relatively small, silent group of patients who mostly live in long-term care facilities. Those being cared for at home form an even more difficult population to reach. The absence of a gold standard for the diagnosis of VS/UWS is another complicating factor. In this context, it is understandable that only 5/14 prevalence figures were (partly) based on verified cases, none according to current expert recommendations. This fact, combined with the possibility that the 9/14 studies pre-dating the definition of the minimally conscious state (MCS) in 2002^[7] may have resulted in a combined prevalence of MCS and VS/UWS together, undermines the reliability of available prevalence figures on VS/UWS. Both inclusion of MCS and failure to identify signs of consciousness might lead to a substantial overestimation of the actual number of VS/UWS patients in reported publications, while incomplete coverage of the various care settings may also cause underestimation.



To our knowledge, only one systematic review has evaluated the prevalence of the VS/UWS before^[62]. It showed heterogeneity in both methodology and outcomes, which our study confirms. However, in contrast, we found 14 instead of 5 eligible prevalence studies and were able to assess the methodological quality of studies and their context as well. These differences can be attributed to a more extensive literature search and the use of established quality criteria for prevalence studies in our study.

A limitation to our study is that 4 possibly relevant papers^[27-30] could not be retrieved, despite attempts to contact the authors and publishers. One of these records is an early Japanese study, in which authors of two studies we did include, were involved^[27]. The abstracts nor contents of the other 3 have been clarified.

In conclusion, the VS/UWS prevalence figures which keep appearing in public debate, influencing health care policy and the public picture, are an unreliable representation of the actual patient population. This calls for new, nationwide point prevalence studies in which patients could be identified by addressing medical professionals in hospitals, rehabilitation centres, nursing homes, facilities for people with intellectual disability and general practitioners. Inclusion criteria should cover VS/UWS due to acute brain injury at least 1 month prior to the study date, as by this time the incidence of complications related to the causative trauma or illness is expected to drop. With regards to diagnosis verification, the value of repeated measurements, which is strongly recommended in clinical practice^[63,64], should be weighed against the methodological challenges of visiting patients as soon as possible after the point prevalence date. A single CRS-R assessment, for example, could be enhanced by the active involvement of proxies and caregivers who observe the patient on a daily basis.

When it comes to VS/UWS, one of the most dramatic conditions we face in modern medicine, it is time to get the epidemiological facts straight.



ACKNOWLEDGEMENTS

Elmie Peters kindly assisted in constructing the search strategy.

SUPPLEMENTARY MATERIAL

A: Search strategies

PubMed

persistent vegetative state[MeSH Terms] OR (vegetative[tiab] AND (state*[tiab] OR status[tiab] OR condition[tiab])) OR (unresponsive[tiab] AND wakefulness[tiab]) OR (coma[tiab] AND vigil[tiab]) OR apallic[tiab] OR (akinetic[tiab] AND mutism[tiab]) OR akinetic mutism[Mesh Terms]

AND

prevalence[MeSH Terms] OR epidemiology[MeSH Terms] OR epidemiology[tiab] OR epidemiology[Subheading] OR epidemiolog*[tiab] OR prevalen*[tiab]

PsycINFO

((vegetative and condition) or (vegetative and state*) or (vegetative and status) or (unresponsive and wakefulness) or (coma and vigil) or apallic or (akinetic and mutism)).

ti,ab.

AND

epidemiology/ or prevalen*.ti,ab. or epidemiolog*.ti,ab.

Cochrane library

((vegetative AND condition) OR (vegetative AND state) OR (vegetative AND status) OR (unresponsive AND wakefulness) OR (coma AND vigil) OR apallic OR (akinetic AND mutism) in Record Title in all products) OR ((vegetative AND condition) OR (vegetative AND state) OR (vegetative AND status) OR (unresponsive AND wakefulness) OR (coma AND vigil) OR apallic OR (akinetic AND mutism) in Abstract in all products) OR MeSH descriptor Persistent Vegetative State explode all trees in all MeSH products



Cinahl

(MH "Persistent Vegetative State") OR TI ((vegetative AND condition) OR (vegetative AND state) OR (vegetative AND status) OR (unresponsive AND wakefulness) OR (coma AND vigil) OR apallic OR (akinetic AND mutism)) OR AB ((vegetative AND condition) OR (vegetative AND state) OR (vegetative AND status) OR (unresponsive AND wakefulness) OR (coma AND vigil) OR apallic OR (akinetic AND mutism))
AND
(MH "Epidemiology+") OR (MH "Prevalence") OR TI (epidemiolog* OR prevalen*) OR AB (epidemiolog* OR prevalen*)

Embase

exp persistent vegetative state/ or ((vegetative and condition) or (vegetative and state*) or (vegetative and status) or (unresponsive and wakefulness) or (coma and vigil) or apallic or (akinetic and mutism)).ti,ab.
AND
exp epidemiology/ OR exp prevalence/ OR ep.fs.

B. Method of quality assessment and data extraction for prevalence studies on VS/ UWS, based on Loney et al.^[17], Graham et al.^[16], and Radulescu et al.^[18].

Title

First author

Year

Study design

- Sampling frame:
 - Country
 - Different geographical region
 - Probability sample
 - Specific population (e.g. nursing home residents)
 - No information
- Sample size:



in relation to the population of which a prevalence is calculated

- Adequate
- Moderate
- Poor
- No information
- Demographic and socioeconomic variables affecting sample:
 - Are described
 - No information
- Probability of sample covering population (in terms of sampling):
 - Is discussed
 - No information

Period/ point prevalence

Inclusion criteria

Exclusion criteria

Response:

- Response rate:
 - (Percentage)
 - No information
- Non responders:
 - Are described
 - No information

In case of estimates:

- Probability of sample covering population (in terms of statistics): *have possible sample bias been statistically corrected?*
 - Is discussed
 - No information
- Confidence intervals
 - Are given
 - No information



Verification of diagnosis by means of on-site assessment

- Proportion of cases validated
 - (Percentage)
 - No information
- Assessment of level of consciousness:
 - CRS-R
 - Other validated scale for level of consciousness
 - Non-standardised description of clinical characteristics
 - No measurement; diagnosis from medical chart
 - No information
- Assessor of level of consciousness:
 - More than one researcher
 - One researcher
 - Treating physician + expert/ second opinion
 - Treating physician
 - Other professional involved with patient
 - No information
- Number of clinical assessments:
 - Repeatedly by different individuals
 - Repeatedly by one individual
 - Once
 - No information
- Best reaction seen by caregivers and/ or proxies
(apart from clinical assessment):
 - Mentioned
 - No information
- Consensus on VS/UWS diagnosis between care professionals and/ or proxies:
 - Mentioned
 - No information

Outcome: prevalence figure

Remarks



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3

THE VEGETATIVE STATE: PREVALENCE, MISDIAGNOSIS AND TREATMENT LIMITATIONS

Willemijn S. van Erp • Jan C.M. Lavrijsen • Pieter E. Vos • Hans Bor • Steven Laureys •
Raymond T.C.M. Koopmans • Journal of Medical Directors' Associations 2016.16(1): 85 e89-85 e14



ABSTRACT

Introduction

Patients in a vegetative state/ unresponsive wakefulness syndrome (VS/UWS) open their eyes spontaneously, but show only reflexive behaviour. While 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 aetiology was hypoxia sustained during cardiac arrest and resuscitation. Over 50% of patients had not received rehabilitation services. Most were given life-sustaining treatment beyond internationally accepted prognostic boundaries regarding recovery of consciousness. Seventeen out of 41 patients (41%) presumed to be in VS/UWS were found to be at least minimally conscious.

Conclusions

Results translate to a prevalence of 0.1–0.2 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.

INTRODUCTION

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 and functional use of objects⁽⁷⁾. Bruno et al. recently argued to distinguish patients who reproducibly follow commands (MCS+) from those who do not (MCS-)^(8,9).

While the neurophysiological substrates of disorders of consciousness are steadily being unravelled⁽¹⁰⁾, their epidemiology remains unclear. In many countries, including the USA and Great-Britain, the prevalence of VS/UWS is unknown⁽¹¹⁾. 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⁽¹²⁾. Uncertainty about the exact number of people in a condition referred to as ‘a fate worse than death’⁽¹³⁾ not only compromises our scientific picture, it can also 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⁽¹⁴⁾. 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 turns out to be at least in MCS when examined with a validated assessment tool^(15, 16).

This paper 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 centres in the Netherlands.

METHODS

The Netherlands is inhabited by 16.7 million people and has a population density of 401 people per square km⁽¹⁷⁾ (in comparison, the USA has a population density of 33.7/km² ⁽¹⁸⁾). 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⁽¹⁹⁾.

In the last week of April, 2012, we contacted medical directors from all of the 635 nursing homes (merged in 187 organisations), 20 rehabilitation centres, 90 hospitals with an intensive care unit, neurology and/or neurosurgery ward and 70 hospices, plus the 270 members of the Dutch Association of ID Physicians via e-mail. The e-mail provided the internationally established diagnostic criteria for VS/UWS⁽³⁾. The addressee was asked whether any patients with this diagnosis at least one month after acute brain injury (e.g. hypoxia, stroke, trauma) were present within the population under the responsibility of the medical staff on May 1st, 2012. Replies were given by e-mail. If a missing response could not be retrieved by telephone, the institution or physician was considered a non-responder.

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^(20,21). Staff and family were invited to the assessment. Any additional behaviour possibly indicative of consciousness they mentioned, for example command-following exclusively on request of a relative, was evaluated for contingency in a structured manner⁽²²⁾. We documented medication, factors of possible influence on the level of consciousness (e.g. infections) that had occurred up to two weeks before the study visit, and asked whether staff or family thought that the patient's state was any different from their normal condition. The time between the last administration of artificial nutrition and hydration (ANH) and the start of the assessment was registered, as patients have been shown to be less responsive shortly after administration of ANH⁽²³⁾. The treating physician was requested to complete a secured online questionnaire about demographic and clinical characteristics, treatment goals and limitations to treatment (e.g. a do-not-resuscitate order). To prevent research participation from interfering with the relationship between the patient's proxies and the treating physician, study findings were communicated only to the latter. The families were notified of this before they gave consent.

Statistics

From the sum of the absolute number of verified and unverified cases of VS/UWS, a prevalence figure of hospitalized and institutionalized VS/UWS patients per 100 000 members of the Dutch population was calculated. Clinical characteristics were analyzed using SPSS 20.0. We calculated means, medians, confidence intervals, standard deviations and percentages where applicable.

Ethical approval

According to the Dutch Medical Research Involving Human Subjects Act (1998), the study did not meet criteria for medical scientific research. The protocol was judged by an accredited medical research ethics committee, which on these grounds decided that no additional ethical evaluation was indicated. Nevertheless, the families of all patients were asked for written informed consent.

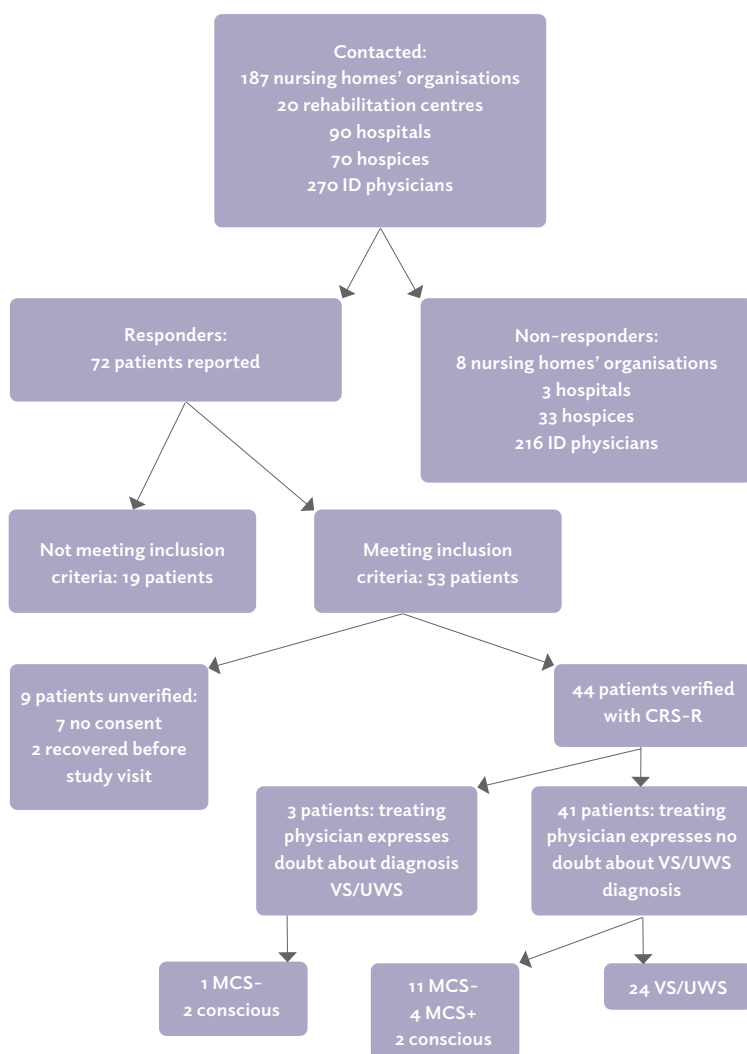


RESULTS

Response rates were 96% for nursing homes, 100% for rehabilitation centres, 97% for hospitals, 53% for hospices and 20% for ID physicians.

A total of 53 patients were reported to be in VS/UWS for at least 1 month after sustaining acute brain injury. Representatives of 46 of them consented to inclusion. The patients were visited with a median time lapse from the point prevalence date of 20 days: 30 patients were seen within 30 days, 14 patients between 30 and 60 days and 2 after over 60 days. We obtained CRS-R scores in all 46 patients. In 38 cases, additional behaviour was reported by medical staff or families and evaluated for contingency. Among the observed personally salient stimuli were proxies' voices, music, family pictures, the smell of chocolate, the presence of a patient's dog and watching a stand-up comedian on TV. Results of the initial inquiry and of the verification are shown in figure 1.

Figure 1. Flowchart showing results of prevalence inquiry and verification



On the day of verification, 2 patients were reported by their physician to have emerged from VS/UWS since the point prevalence date. Both had sustained neurological damage due to subarachnoid haemorrhage. According to their respective physicians, one had

been in VS/UWS up until 2 months after the incident (4 days after the point prevalence date), and the other up to 10 months (30 days after the point prevalence date). Testing by means of the CRS-R 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 out 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 two were conscious, as demonstrated by the ability of functional use of objects and/or functional communication (table 1).

Table 1. Signs of consciousness in patients with doubtful diagnosis

Treating physician's diagnosis	Consensus; agreement on diagnosis between staff and proxies	CRS-R	Structured observation	Researcher's diagnosis
Doubt	No; proxies consider behaviour to be reflexive, staff has doubts	Object manipulation	Manipulates poker chips exclusively	MCS-
Doubt	No; proxies and physical therapist consider movements to be non-reflexive, physician has not witnessed this	Reproducible movement to command, functional use of object (spoon) only on request of proxy	No additional findings	Conscious
Doubt	No; proxies experience functional verbal communication, staff has not witnessed this	Functional communication only with nephew	No additional findings	Conscious



Seventeen out of 41 patients with a reported clinical diagnosis of VS/UWS (41%*) 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 vocalisation when presented with an ice-cream. The other patients' conscious behaviour had not been witnessed by staff before (e.g. communication only with a nephew) or had been seen but not been recognized as a sign of consciousness (e.g. 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).

Table 2. Signs of consciousness in misdiagnosed patients

Treating physician's diagnosis	Consensus; agreement on diagnosis between staff and proxies	CRS-R	Structured observation	Researcher's diagnosis
VS/UWS	Yes	Visual following	No additional findings	MCS-
VS/UWS	Yes	Visual following	No additional findings	MCS-
VS/UWS	Yes	Visual following	No additional findings	MCS-
VS/ UWS	Yes	Visual following	Laughs appropriately during stand-up comedian's conference on tv	MCS-
VS/UWS	Yes	Reflexive behaviour	Smiles in response to ice cream, screams when ice cream is removed, smiles when returned 4/4 trials	MCS-
VS/UWS	Yes	Localisation of noxious stimuli	Fumbles with sheet	MCS-
VS/UWS	No: proxies experience eye contact	Visual following	No additional findings	MCS-
VS/UWS	No: proxy experiences functional communication by means of sighs and facial expression	Visual following	No additional findings	MCS-

* percentage corrected in erratum



VS/UWS	No: proxies experience eye contact	Visual following, automatic motor response	No additional findings	MCS-
VS/UWS	No: proxies and nurses consider ball catching non-reflexive	Object localisation (reaching), localisation of noxious stimuli	Catches a ball thrown horizontally from 2m distance	MCS-
VS/UWS	No: paramedics consider reactions to visual stimuli to be non-reflexive	Object recognition, automatic motor response	No additional findings	MCS-
VS/UWS	Yes	Reproducible movement to command, visual following, object manipulation, intentional communication when asked for by proxy	No additional findings	MCS+
VS/UWS	Yes	Reproducible movement to command, visual fixation	Visual fixation on childrens' picture	MCS+
VS/UWS	No: proxies consider smiles to be non-reflexive	Reproducible movement to command, object recognition	Shakes researcher's hand	MCS+
VS/UWS	No: proxies experience eye contact	Reproducible movement to command, object localisation (reaching), automatic motor response	No additional findings	MCS+
VS/UWS	Yes	Consistent movement to command, object recognition, functional use of object (toothbrush), functional communication when asked for by proxy	No additional findings	Conscious
VS/UWS	No: proxies and speech therapist report functional use of objects and command following, unwitnessed by physician	Systematic movement to command, object localisation (reaching), functional use of objects (spoon, toothbrush) only on request of speech therapist	No additional findings	Conscious



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

Patient characteristics

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. Tracheostomy was present in 8 cases (33%); 5 were cuffed, 3 non-cuffed. This group had sustained the causative injury relatively recently (mean 1y8m) when compared to the group without tracheostomy (mean 6y8m). All patients received ANH via percutaneous endoscopic gastrostomy (PEG), 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.

Table 3. Basic characteristics of verified VS/UWS patients

Sex (%)		Female: 12 (50%) Male: 12 (50%)
Age	• Mean (SD)	51y (13y)
	• Range	27–73y
Marital status		Single: 9 (38%) Married: 12 (50%) Partner, unmarried: 3 (12%)
Location (%)		Nursing home: 20 (83%) Institution for people with intellectual disability: 2 (9%) Hospital: 2 (9%) Rehabilitation centre: 0 (0%) Hospice: 0 (0%)
Time lapse since incident	• Mean (SD)	5y (6y)
	• Range	1m – 25y
Etiology (%)		Non-traumatic: 16 (67%) Traumatic: 7 (29%) Both: 1 (5%)



**Causes of hypoxic encephalopathy (n=12)
(includes patient with both traumatic and non-traumatic etiology)**

*Cardiogenic shock: 7
Septic shock: 2
Hypovolemia: 1
Accidental asphyxia: 1
Unknown: 1*

Other non-traumatic causes (n=5)

*Subarachnoid haemorrhage: 3
Tuberculous meningitis: 1
Dengue-fever and overcorrection of hyponatraemia 1*

Traumatic causes (n=8) (includes patient with both traumatic and non-traumatic etiology)

*Traffic accident: 6
Fall: 2*

Four patients (17%) were within internationally accepted prognostic boundaries: this is, 3 months after non-traumatic and 12 months after traumatic causes⁽³⁾. The other 20 patients had been in VS/UWS for on average 6 years (SD 6y2m); 2 non-trauma for 3-12 months, 10 for 1-5 years, 5 for 5-10 years and 3 for over 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' (i.e. aimed at quality of life, may include life-prolonging therapies) in 13 patients, 'curative' (i.e. aimed at recovery of consciousness) in 5 patients, 'symptomatic' (i.e. 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 re-admitted to the intensive care unit and 9 were not to be re-admitted 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 (i.e. sensory stimulation therapy⁽²⁵⁾) or regular rehabilitation programme.



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 0.1–0.2 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 to the present, the most striking difference is in aetiology. 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 aetiology 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^(11,12). This may be attributable to end-of-life decisions in the acute phase of severe brain injury⁽²⁶⁾, as well as in post-acute and long-term care settings⁽²⁷⁾. In the 1990's an ethical, medical and legal 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^(28,29) and violates human dignity⁽³⁰⁾. In practice, withdrawal of ANH is allowed beyond 3–6 months after non-traumatically and 12 months after traumatically induced VS/UWS. The decision to withhold or withdraw medical treatment is made by the physician^(30,31). Still, in 20 out 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^(31, 32).

Remarkably, one of the patients in this study was reported to have emerged from VS/UWS 10 months after the occurrence of non-traumatic brain injury. Recent publications show that the aforementioned prognostic boundaries may be outdated⁽³³⁾. 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, organising 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 programme in one of two 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⁽³⁴⁾, the fact that a country allows cessation of treatment without enabling patients to first fully explore their means of recovery, raises questions.

Seventeen out of 44 patients (41%*) 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 centres^(15, 16). 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⁽³⁵⁻³⁸⁾ and appear to process emotional, auditory and nociceptive stimuli in a way very similar to that of healthy individuals^(39, 40). Underestimating their level 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 only occurring in reaction to very specific stimuli. In others, conscious behaviour was wrongfully labelled 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⁽⁴¹⁾ 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 centres 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 hospices 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, i.e. that respondents based their reply on incomplete information. If this were the case, the actual number of patients may be higher. On the other hand a more extensive verification protocol might have detected signs of consciousness in certain patients, specifically those in whom factors like infections, sedatives and recent administration of ANH were present. Still, our single-observer on-site verification method covered a complete country within a median of 20 days after the point prevalence date. The active involvement of patients' proxies and staff enriched the assessment: in all but one of the cases in which proxies disagreed on the treating physician's diagnosis of VS/UWS, the family and/ or a nurse who knew the patient well were present.

RECOMMENDATIONS

Providing good care for patients with a rare, complex condition in a context of scattered expertise, paucity of diagnostic and therapeutic guidelines and scarce resources is challenging. Nonetheless, patients with disorders of consciousness deserve tailored



medical care in accordance with up-to-date scientific and psychosocial standards. Our study shows that at this moment, patients in VS/UWS and related conditions are at substantial risk of being misdiagnosed and of being denied rehabilitation. The number of patients appears to be too small for non-specialized 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 could also assure liaison between hospitals, rehabilitation centres 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.



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4

THE UNRESPONSIVE WAKEFULNESS SYNDROME: DUTCH PERSPECTIVES

Willemijn S. van Erp • Jan C.M. Lavrijsen •

Raymond T.C.M. Koopmans • Nederlands Tijdschrift voor Geneeskunde 2016;160: D108



ABSTRACT

The unresponsive wakefulness syndrome (UWS), formerly known as the vegetative state, is one of the most dramatic outcomes of acquired brain injury. Patients in UWS open their eyes spontaneously but demonstrate only reflexive behavior; there are no signs of consciousness. Research shows that, for years now, the Netherlands has had the world's lowest documented UWS prevalence. Unfortunately, this small group of vulnerable patients does not receive the care it needs. Access to specialized rehabilitation is limited, misdiagnosis rates are high and a substantial number of UWS patients receive life-prolonging treatment beyond chances of recovery, despite a framework allowing for discontinuation of such treatment once recovery of consciousness has become unlikely. By comparing data from 2012 with those of 2003, this paper illustrates the current situation and perspectives for UWS patients in the Netherlands and makes recommendations for the optimization of treatment and care, as well as for future research.



The unresponsive wakefulness syndrome (UWS), formerly known as ‘the vegetative state’⁽¹⁾ is one of the most dramatic outcomes of acquired brain injury. After coma, a patient in UWS shows spontaneous eye opening and independent respiration, but no evidence of consciousness⁽²⁾.

In March 2016, a large part of the International Brain Injury Association World Congress in The Hague was dedicated to UWS patients and their proxies. Rightfully so: although UWS has been the subject of societal debate since the 1990’s, many knowledge gaps remain. The epidemiology of UWS is largely unknown: in most countries, its prevalence can only be estimated⁽³⁾. The Netherlands, however, form a positive exception in this respect. Already in 1985, the Dutch UWS population, then counting 53 patients, was subject of publication⁽⁴⁾. In 2003, a prevalence study was carried out in nursing homes nationwide and in 2012, a new study involved all medical institutions, from hospital to hospice and from nursing home to institution for people with intellectual disability^(5, 6). With two patients per million inhabitants at most, the Netherlands have had the lowest documented UWS prevalence in the world for years⁽³⁾.

In this paper, we compare the results of the 2003 and 2012 studies. We describe the current state of affairs and perspectives regarding UWS in the Netherlands and make recommendations for future research and optimization of treatment and care.

The unresponsive wakefulness syndrome in the Netherlands: 2003 versus 2012

Table 1 shows the results of the 2003 and 2012 studies. The absolute number of UWS patients remained virtually unchanged: 32 versus a maximum of 33 patients. It has to be taken into account that in 2003, only a small proportion of reported patients had their diagnoses verified by the researchers. Still, UWS does not appear to have become more, or less, prevalent. What *has* increased, is the percentage of patients in UWS following hypoxic encephalopathy; in 9 years time, this went from 23 to 50% of the population. In 2012, half of the patients in UWS were in that state after surviving a resuscitation.



Table 1. Characteristics of UWS patients in the Netherlands in 2003 and 2012

	2003	2012
Number of patients	32 (3 verified)	33 (24 verified)
Prevalence	0,2/100.000	0,1-0,2/100.000
Sex	73% female	50% female
Age; mean in years (SD, range)	53 (22, 9-90)	51 (13, 27-73)
Location	100% nursing home (other institutions were not involved)	82% nursing home 9% ID- institution 9% hospital 0% rehabilitation center
Etiology		
Non-trauma; %	73	67
Stroke*	47	0
Hypoxic encephalopathy	23	46
Subarachnoid hemorrhage	-	12
Miscellaneous	3	9
Trauma; %	27	29
Both trauma & non-trauma; %	-	4†
Time post-ictus; mean years (SD)	6 (6)	5 (6)
Administration of nutrition and hydration; n	26 PEG 5 nasogastric tube 1 partially oral‡	32 PEG 1 nasogastric tube§
Rehabilitation	Unknown	46%
Treatment restrictions in patients beyond chances of recovery; n (Total: n=20)	Unknown	4 none 16 no resuscitation 14 no ventilation 9 no ICU 8 no hospital 4 intention to withdraw artificial nutrition and hydration



Misdiagnosis	Unknown	17 out of 44 patients: 11 minimally conscious without evidence of language function 4 minimally conscious with evidence of language function 2 conscious
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Legend: ID = intellectual disability; PEG = percutaneous endoscopic gastrostomy.

* Strokes were not identified as a causal etiology in 2012, with the exception of subarachnoid hemorrhage. In 2003, no distinction was made between different kinds of stroke.

† Patient sustained hypoxic encephalopathy following trauma

‡ One patient was fed by her mother, using a teaspoon. In 2003 this was considered reflex behavior.

§ No PEG as hospital re-admission was considered inappropriate in this patient

The average age did not change (53 versus 51 years) but showed a narrower range in 2012: in contrast to 2003, no underage patients were identified. This may be related to personalized funding which in recent years has allowed for young patients to receive care at home. Children may also be more likely to be admitted to institutions for people with intellectual disability. The response rate for this sector, however, was only 20% while of the hospitals, nursing homes and rehabilitation centers, 97% cooperated.

In the 2012 study, we aimed at diagnosis verification in all included patients. We found 41%* of presumed unresponsive patients to show signs of consciousness. The distinction is clinically relevant; minimally conscious patients have better chances of recovery. They can show functional improvement beyond a year after their injury, and process auditory, nociceptive and emotional stimuli in a neurophysiologically near-normal manner⁽⁷⁻¹²⁾. In order to detect signs of consciousness in daily practice, no expensive or complex techniques are necessary. The basis is structured clinical observation, using the ‘Coma recovery scale-revised’^(13, 14). This scale is reasonably easy to learn and apply, especially for



professionals familiar with the Glasgow coma scale. An extensive article about level of consciousness determination in patients who do not or not fully regain consciousness after coma is to be published soon⁽¹⁵⁾.

In 2003, patients were on average about the same length of time in UWS as in 2012; during the nine years in between, all but one patient died. Only one individual included in 2003 was identified again in the 2012 study: a man who had contracted his traumatic brain injury at the age of 18 and was still in UWS 25 years later. The new data show that to this day, a considerable number of patients receives life-sustaining treatment for a prolonged period of time (table 2).

Table 2 Prolonged survival of UWS patients in 2003 and 2012

Survival	Number of patients	
	2003	2012
1-5 years post-ictus	13	10
5-10 years	8	5
> 10 years	5	3

Ethical questions

These findings also raise ethical questions. In the 1990s, the Health Council of the Netherlands and the Royal Dutch Medical Association stated in successive reports that life-prolonging treatment in UWS does not serve the patient's interests when there is no chance of recovery of consciousness^(16, 17). The responsibility for (dis-)continuation of treatment - including the administration of artificial of nutrition and hydration - lies with the treating physician. Most patients in our study had treatment limitations in place, such as a do not resuscitate order. In four patients, the doctor expressed the intention



to discontinue the administration of artificial nutrition and hydration in the future. To all patients who had been in UWS for over 5 years, treatment restrictions applied. However, there were also two patients with a fully active, unrestricted policy, including resuscitation, artificial respiration and admission to the intensive care unit, while their injury had occurred over 12 months prior. By then, no recovery of consciousness is expected.

Another finding is that UWS patients in the Netherlands have limited access to rehabilitation, in contrast to the situation in other Western countries^(8,19). The effect of so-called early intensive neurorehabilitation in this small and heterogeneous patient population has not yet been established through randomized, controlled and blinded trials. However, it is clear that specialized care for patients with disorders of consciousness results in better control of complications, family guidance and diagnostic accuracy⁽¹⁹⁻²¹⁾.

In the Netherlands, early intensive neurorehabilitation in a specialized rehabilitation center is only reimbursed for patients up to 25 years of age. Although two nursing homes offer a similar program, in 2012 over 50% of the presumed unresponsive patients admitted to long-term care had never followed any form of rehabilitation. In spring of 2016, the Dutch National Health Care Institute advised the Minister of Health, Welfare and Sports to conditionally allow specialized rehabilitation for patients over 25 years of age (<https://www.zorginstituutnederland.nl/publicaties/rapporten+en+standpunten>).

Future perspectives

The Netherlands combines high-quality hospital and rehabilitation medicine, good access to nursing homes with formally trained elderly care physicians, and a tradition of openly discussing ethical issues. If anywhere, a chain of care for the small group of complex patients with prolonged disorders of consciousness could and should be in place here. However, the already limited perspective of these vulnerable patients in our country is further narrowed by inadequate access to suitable diagnostics and treatment. Only a minority of patients has access to specialized rehabilitation and underestimation of level of consciousness occurs regularly.



Over 15 years after the establishment of clear frameworks for discontinuation of life-sustaining treatment in UWS beyond chances of recovery, a considerable number of patients remains in prolonged UWS. This kind of decision-making requires a lot from both the physician and the patient's relatives, and is complex and morally charged in the context outlined above. A decision about discontinuing a treatment loses its foundation if the diagnosis, which is the starting point of every treatment, is incorrect and the treatment itself is suboptimal^(22, 23). An expertise network is currently working on the framework for suitable care for patients with prolonged disorders of consciousness, linked to the development, application and exchange of knowledge. We advocate the establishment of a mobile team of experts to provide advice at national level with regards to diagnosis, treatment and medical-ethical dilemmas.

Now that the post-acute and chronic phases of UWS in the Netherlands have been described, we have a starting point for in-depth questions. What roles do the physician and the patient's family play in allowing life-prolonging treatment to continue? How do diagnostic uncertainty and suboptimal post-acute care influence this decision-making process? What is the long-term course of UWS? In the coming years these themes will be the focus of a cohort study.

The fact that in the Dutch healthcare practice not everything that can be done, has to be done, is a great merit⁽²⁴⁾. But in the case of patients with prolonged disorders of consciousness, we must ensure that everything *can* be done in the first place, especially prior to life and death decisions. With the right diagnostics, optimal exploration of possibilities for recovery for everyone and honest conversations about treatment goals and limitations - starting in the acute phase - in the Netherlands ultimately no one has to remain in UWS.



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5

THE UNRESPONSIVE WAKEFULNESS SYNDROME: OUTCOMES FROM A VICIOUS CIRCLE

Willemijn S. van Erp • Jan C.M. Lavrijsen • Pieter E. Vos • Hans Bor •
Steven Laureys • Raymond T.C.M. Koopmans • *Annals of Neurology* 2020;87(1):12–18.



The unresponsive wakefulness syndrome, also known as the vegetative state (VS/UWS), is one of the most dramatic outcomes of acquired brain injury. Despite spontaneous eye opening and independent vital functions, VS/UWS patients cannot functionally communicate their thoughts or feelings and appear completely unaware of their surroundings and themselves^(1,2). VS/UWS has confronted families, clinicians, society and science with a variety of clinical and ethical quests and dilemmas for over 50 years^(3,4).

Uncertainty about the natural course of VS/UWS plays a major part in many of these challenges. With a prevalence of 0.2 to 6.1 patients per 100.000 inhabitants⁽⁵⁾, it is classified as a rare to ultra-rare medical condition⁽⁶⁾. Available figures on recovery and survival arise mostly from well-organized clinical environments in which VS/UWS patients receive specialized post-acute care⁽⁷⁻⁹⁾. These, however, do not represent standard practice^(10,11). Fins coined the term ‘disordered care’ to describe the dire straits patients with disorders of consciousness and their families in the USA were in in 2013⁽¹⁰⁾. The evidence with regard to the expected outcome in patients in VS/UWS was characterized as ‘limited’ in a 2018 review by the American Academy of Neurology (AAN)^(12,13).

Data about survival and end-of-life scenarios in VS/UWS are of particular importance to the ongoing international debate on decision-making in prolonged disorders of consciousness (PDOC). The view on discontinuation of artificial nutrition and hydration (ANH) in these patients varies greatly between countries^(4,11,14-17). Although in the United States, discontinuation of ANH has been lawful since the Cruzan ruling in 1990⁽¹⁸⁾, the responsibility for clinical decision-making lies with the incapacitated patient’s surrogates and may involve the court (e.g. the case of Terri Schiavo⁽¹⁹⁾). The United Kingdom recently moved the responsibility for end-of-life decisions in PDOC from the courtroom back to the clinic^(20,21). In France, the summer of 2019 brought a tug of war about the discontinuation of ANH in a patient who had been in VS/UWS for 11 years⁽²²⁾. Those involved in, or confronted by, such paradigm shifts and public discussions, are in need of clear scientific descriptions of how VS/UWS patients fare in real-life settings.

Since the 1990’s, a medical-ethical-legal framework in the Netherlands has allowed for



withdrawal of ANH in VS/UWS once chances of recovery of consciousness have become negligible^(4, 23, 24). Contrary to the US, in the Netherlands the responsibility for such decisions lies with the treating physician. Up until 2019 specialized PDOC rehabilitation was only reimbursed for patients younger than 25 years. Next to this threshold for post-acute rehabilitation, over the years a highly professional long-term care practice developed. A specific academic medical specialty for working in nursing homes and in primary care was established. This medical discipline, called ‘elderly care medicine’ (formerly known as nursing home medicine), is dedicated to patient-centered care for the elderly, but also for young patients with the severest sequelae of neurological diseases^(25, 26). Dutch elderly care medicine has a tradition of research whose topics include VS/UWS. Specifically, decision-making and end-of-life scenarios in VS/UWS have been studied retrospectively and in case reports since the 1990’s⁽²⁷⁻³¹⁾.

The Netherlands have the lowest VS/UWS prevalence documented worldwide^(5, 32). Nonetheless, prolonged and extremely prolonged VS/UWS, even beyond 25 years after the causative injury, occurs as well, often associated with conflicts between relatives and medical staff about life-prolonging medical treatment⁽²⁹⁻³²⁾.

A nationwide dynamic cohort study, carried out between 2012 and 2018, allows us to present the outcomes of VS/UWS patients in this particular context. Extensive descriptions of the study methods and results are available as supplementary material.

The study involved hospitals, rehabilitation centers, nursing homes, and patients cared for at home. Level of consciousness was quantified with the Coma Recovery Scale-Revised (CRS-R)⁽³³⁾, at inclusion and during up to six years of follow-up by the same formally trained and experienced clinician (WvE). Patients’ families were invited to actively participate in the assessment. Treating physicians provided their patients’ clinical characteristics. Patients’ trajectories through the healthcare system and aspects of the care they received were recorded 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 which are difficult to catch in questionnaires⁽³⁴⁾. Physicians were also invited to share any challenges, positive experiences or peculiarities they had encountered while caring for the included patient.

As VS/UWS is extremely rare in the Netherlands⁽³²⁾, we allowed for variable time post-ictus at inclusion and scheduled follow-up accordingly. 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 3 years post-ictus would be assessed once a year.

Over the course of 6 years, 59 patients possibly eligible for inclusion were clinically evaluated by the researcher: 28 of them (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. Nineteen patients (61%) were included within one year after the incident and 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 (10/31 patients – 32% of the total group).

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 was made in 11 cases (39%). There was no mention 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.



During the total course of the study, six patients emerged from VS/UWS (see supplementary material for the extensive methodology and results). 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 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). We will now zoom in on the data we obtained in relation to the end of life in VS/UWS patients.

Scenarios of dying are listed in table 1. 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 case. Another 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 of 18 deaths (50%) occurred after withdrawal of ANH.

Table 1. End-of-life scenarios in deceased VS/UWS patients (n=18)

Sex, age	Etiology	Time post-ictus (years, months)
Cessation of ANH		
M, 45	TBI	4m
M, 57	OHCA	5m
M, 45	OHCA	5m
F, 44	TBI	9m
M, 26	Non-TBI miscellaneous	1y
F, 55	Non-TBI miscellaneous	7y, 4m
F, 50	SAH	7y, 4m
F, 38	TBI	20y
F, 59	OHCA	33y, 5m
New life-threatening complication, no treatment		



F, 65	Non-TBI miscellaneous	1y, 1m
M, 66	OHCA	1y, 2m
New life-threatening complication, died despite treatment		
F, 66	OHCA	5y, 3m
Unexpected death of unknown cause		
F, 29	Non-TBI miscellaneous	5m
F, 52	Non-TBI miscellaneous	1y, 9m
F, 54	SAH	9y, 6m
Missing		
F, 35	OHCA	4m
M, 50	TBI	8m
M, 55	OHCA	4y, 5m

Legend: ANH, artificial nutrition and hydration; F, female; M, male; non-TBI, non-traumatic brain injury; OHCA, out-of-hospital cardiac arrest; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage.

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. A 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 facility). In the other two, a dysfunctional feeding tube led to ANH being withdrawn. All physicians considered themselves responsible for this decision; three of them felt they shared responsibility with the patient’s relatives. According to the physicians, none of the decisions was 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⁽³⁵⁾.

How do these observations relate to what was already known about dying in PDOC? Somatic complications are associated with mortality in VS/UWS, either despite treatment or after a decision to withhold treatment^(29, 30, 36). In a retrospective Dutch study on 43 VS/UWS deaths between 2000 and 2003, death after withholding treatment for a new complication was the primary scenario, in 56% of cases⁽³⁰⁾. A decade later, the primary scenario at the end of life in VS/UWS patients in the Netherlands has become death after withdrawal of ANH, in 50% of cases. This is a substantial increase compared to 2000–2003, when this happened in only 21% of deaths⁽³⁰⁾.

Dutch law states that any medical treatment has to be in accordance to medical professional standards and requires the patient’s consent, or that of their surrogate⁽³⁷⁾. It is the treating physician’s responsibility to ensure that the treatment he or she provides meets both criteria. In unresponsive patients receiving medical treatment in the form of ANH, this reverse burden of proof is complex in two ways.

First, the medical professional standard regarding ANH in VS/UWS is not entirely clear. As we mentioned above, in the late 1990’s authoritative Dutch reports stated that ANH



should not be continued if it at best results in prolonging life in VS/UWS without chances of recovery^(4,23,24). The exact moment those chances have passed, however, cannot be marked with certainty. Although the recent AAN guideline states that a patient's prognosis should not be considered poor within the first 28 days post-injury, it does not explicitly mention when recovery *does* become unlikely⁽¹²⁾. It is now generally accepted that patients may recover consciousness well within the second year after their injuries^(12,38), but their functional outcome, let alone quality of life, is unknown. Moreover, there is no gold standard for the diagnosis of VS/UWS. Clinical misdiagnosis occurs in about 40% of cases^(32,39,40). To complicate things further: even amongst adequately assessed VS/UWS patients, in a significant proportion brain activity patterns compatible with higher cognitive function can be detected with advanced diagnostic techniques⁽⁴¹⁻⁴³⁾. Such techniques are not yet part of routine clinical care. In other words: in trying to predict the yield of ANH in VS/UWS in a purely medical sense, a physician faces serious diagnostic and prognostic uncertainty.

Second, the process of determining whether an individual patient in clinical VS/UWS would have given consent to receive ANH is challenging. The patient cannot speak for themselves. The family is invariably struck by a combination of hope, grief and uncertainty, and sometimes feelings of guilt and anger, that shows parallels with the emotions relatives experience in missing persons' cases⁽⁴⁴⁾. This further aggravates the already complex task of speaking on behalf of a loved-one. Shared-decision making takes time and skills, especially in prolonged disorders of consciousness^(10,13,28,29,45,46) and requires adequate psychosocial guidance of the patient's family. In addition, the family must weigh the same uncertain diagnostic prognostic information the physician has at their disposal.

In our study, the decision to discontinue ANH was made by the physician; never by a junior doctor or resident, and, according to the physicians involved, never against the relatives' wishes. Although the physicians in our cohort considered it their responsibility to discontinue ANH, in all nine cases the timing of ANH withdrawal was linked to a specific and sometimes seemingly haphazard event such as a new complication or a dysfunctional PEG-system. The timeframe in which life-prolonging treatment in VS/UWS may be



stopped, also called ‘the window of opportunity’, is classically situated in the first year after onset^(47,48). In our study, however, we observed such decisions being made in patients in extremely prolonged VS/UWS as well, even after over 33 years. It seems that these heavy deliberations require the momentum of an external trigger, and that that trigger may even appear after decades of status quo.

Dying after discontinuation of ANH has been described as peaceful and calm in previous publications^(27,29,36,49,50), and this is an observation shared by various physicians in our study too. Some patients, however, developed seizures after the sudden discontinuation of anti-epileptic drugs, while others’ bodies changed unrecognizably due to emaciation. Especially when a prolonged period of time, up to 18 days, went by between the moment of ANH withdrawal and the patient passing away, physicians described a ‘burden of witness’⁽⁵⁰⁾ as experienced by both themselves and the patients’ families. In three cases, they even considered this process to have compromised the patient’s dignity. Symptomatic treatment, including palliative sedation is unlikely to relieve this burden⁽⁵¹⁾. In the absence of a patient’s own willful and consistent request for active life termination, and of definite unbearable suffering without perspective of improvement, euthanasia is illegal in the Netherlands⁽³⁵⁾. The question remains whether a *family’s* suffering could ever be reason to discard these requirements, or that that would lead to a slippery slope.

Our cohort of 31 VS/UWS patients in the Netherlands paints a bleak picture of the situation of some of the most vulnerable patients in modern neurological practice. Seventy-nine percent received an incorrect and/ or outdated diagnosis at hospital discharge. Only one patient was allowed specialized clinical rehabilitation. Patients emerging to (minimal) consciousness were far outnumbered by those who died, and 50% of VS/UWS deaths were preceded by a physician’s decision to discontinue ANH.

Our study also testifies of the challenges of investigating an ultra-rare condition with a high mortality in the absence of adequate routine diagnostics, in a context of fragmented care without a central registry. Recruitment proved difficult and some patients were lost even after years of follow-up. It is likely that we missed possible



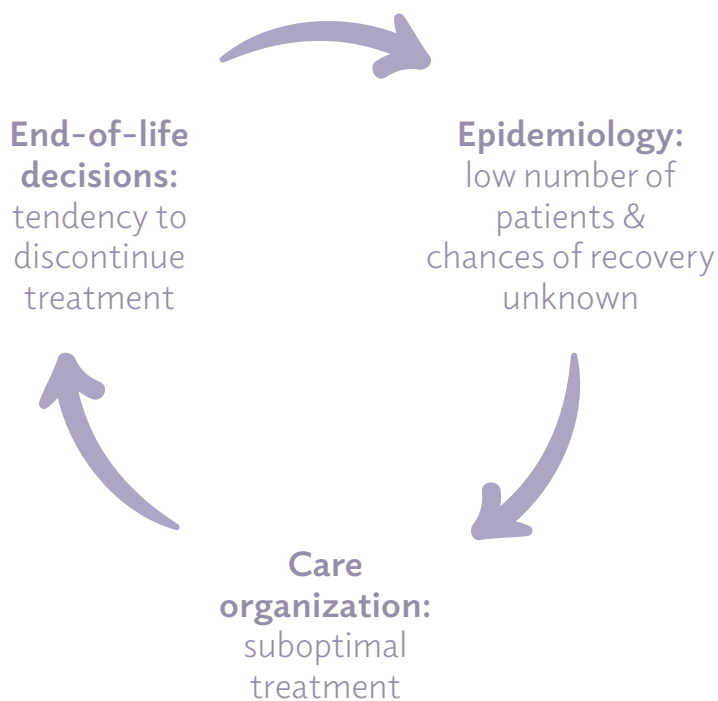
inclusions in patients recovering relatively soon after their injuries. Kaplan-Meier curves and recovery rates could not be calculated due to variable times post-ictus at inclusion and inclusion bias. Moreover, single assessment-based determination of level of consciousness has been associated with diagnostic error⁽⁵²⁾, especially if no accessory diagnostics are deployed. The possibility of having underestimated the included patients' level of consciousness becomes greater when we consider the fact that in only 9% of CRS-R assessments, no factors possibly influencing the measurements were identified. However, research publications on VS/UWS populations have rarely taken such factors into account, nor have repeated assessments (e.g. 5 measurements within 14 days⁽⁵²⁾) been deployed in nationwide, prospective studies.

'Why bother' one might ask, 'investing in future epidemiological research on PDOC anyway?'

To answer this harsh but fair question, we should first acknowledge that modern medicine has a special obligation to patients who survive the worst kinds of acquired brain injury with PDOC. After all, if it weren't for the medical-technological advances of the past 50 years, none of these individuals would have survived in the state they are in. Unfortunately, in many cases this survival leads to a vicious circle. In VS/UWS, epidemiology, organization of care and end-of-life decisions are strongly interconnected (figure 1). Step 1: the group of patients *seems* small and recovery is rarely witnessed, especially by those responsible for care in the acute phase. Step 2: because of the supposed small numbers and modest chances of meaningful recovery, care is organized ad-hoc, resulting in misdiagnosis, shattered expertise, lack of specialized rehabilitation and family counselling. Step 3: decisions about whether or not to continue life-supporting treatment are made without solid diagnosis or scientifically sound prognostics, often by a physician without knowledge of the possible long-term outcomes and without a concrete roadmap to adequate post-acute and long-term care. This brings us back to step 1: the number of patients and their chances of recovery remain small due to a tendency to discontinue life-prolonging treatment, while those who survive continue to receive suboptimal care.



Figure 1. The vicious circle of unknown epidemiology, suboptimal care and tendency to discontinue treatment in VS/UWS



In order to break this vicious circle, recommendations flowing from our study results address clinicians, scientists and policy makers and revolve around three themes. First of all, patients with prolonged disorders of consciousness deserve accurate and timely diagnoses. The distinction between VS/UWS and MCS is of major clinical importance: minimal signs of consciousness are associated with intact nociception and better chances of recovery^(12,53), but also translate to different ethical considerations. A mobile, outreaching team of experts could provide routine on-site CRS-R assessments and refer patients to specialized diagnostic facilities while simultaneously instructing local staff and relatives on behavioral signs of consciousness. It would seem useful to anonymously



store these data in a central registry, so that up-to-date prevalence, incidence and other epidemiologic outcomes would become available. Second, physicians must be facilitated to reach specific competencies needed in PDOC care, for example diagnostics, therapeutic regimes, interdisciplinary collaboration, informing and guiding the patient's family, and end-of-life decisions, when (or preferably before) they are put in charge of such patients. Third, the way in which treatment decisions are made by physicians, how they are experienced by the families involved, and what their results are in terms of quality of life and quality of dying, have been described in monographs (e.g.⁽⁴⁶⁾) but must be studied further using qualitative and quantitative methods combined. Such studies could identify the critical factors contributing to relatively early, late and absent treatment decisions, and help construct the optimal trajectory for decision-making in PDOC along the chain of care that supports patients, families and health care professionals alike, as recommended in recent guidelines and reports from the AAN, the Royal College of Physicians, and the Brain Foundation Netherlands^(12, 20, 54).

That critical decisions about the medical treatment of some of the most helpless patients in modern medicine can be made by dedicated physicians, in close deliberation with those patients' relatives and without judicial, legal or media interference, can be considered a merit. However, the very responsibility that comes with this merit compels us to also provide optimal facilitation of recovery during the period of time when that recovery might take place. Patients' potential must be supported with the same personalized care and compassion as the decision to discontinue treatment when that hoped-for recovery does not occur. With adequate collaboration between scientists, clinicians and policy makers, neither patients with prolonged disorders of consciousness, nor their families, should have to fall between the cracks of a disordered care system.



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SUPPLEMENTARY MATERIAL

A. 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.

B. 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.



Table A. 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 No relationship	20 (65%) 11 (35%)
Patient's representative	Partner Parent Child Other	16 (52%) 8 (26%) 4 (12%) 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 • OHCA • SAH • Surgical complications • Miscellaneous non-trauma Trauma • Traffic accident • Fall • Sports injury	22 (71%) 12 (10 cardiac cause) 3 3 4 9 (29%) 6 (4 car, 2 bicycle) 2 1
Invasive devices	Tracheostomy • Cuffed • Uncuffed Artificial nutrition and hydration • Nasogastric tube • PEG • PEG – jejunal Urinary catheter 16/31	16 (52%) 8 8 31 (100%) 5 24 2 16 (52%)
Location at inclusion	Nursing home Neurology ward in hospital Transfer unit in hospital At home	26 (84%) 3 1 1
Treating physician	Elderly care physician Resident Junior doctor Neurologist General practitioner	18 (58%) 6 4 2 1
Rehabilitation	No rehabilitation Specialized rehabilitation in clinical rehabilitation centre Specialized rehabilitation in nursing home Does not apply, patient still in hospital	20 4 (3 abroad) 4 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.

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 A). 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.



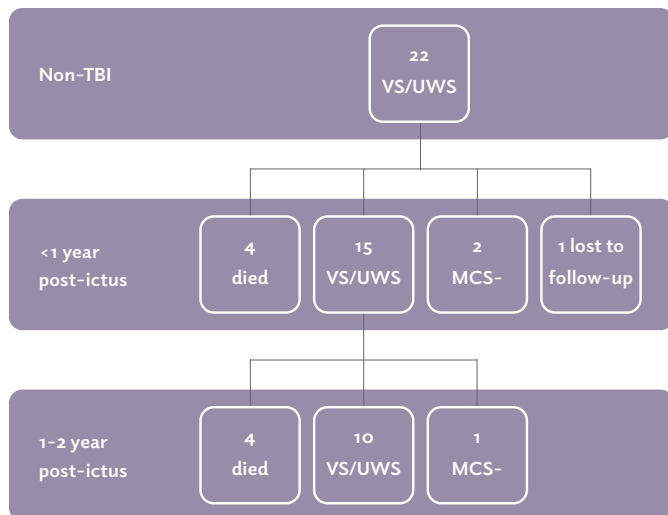
The treating physician was an elderly care physician in 18/31 cases (58%), a resident or junior doctor in ten (32%), a neurologist in three cases and a general practitioner in one case.

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.

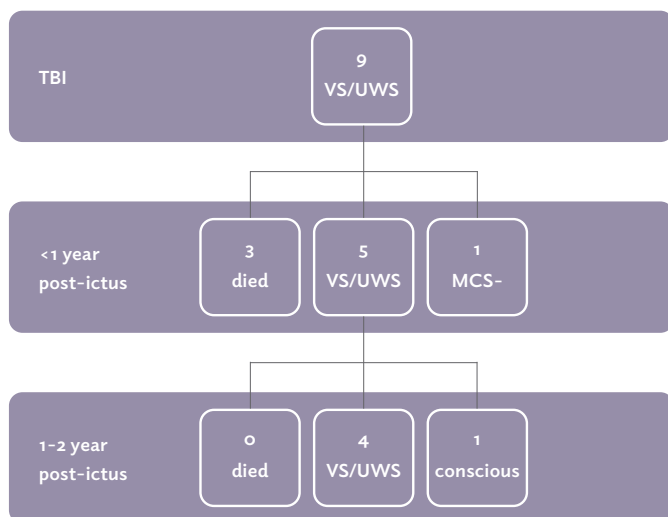
Outcome data are as follows. Out of the 22 non-TBI patients, eight (36%) died within two years post-ictus and three (14%) emerged to MCS without command following (figure A). Of the nine traumatic VS/UWS patients, four (44%) died, one emerged to MCS without command following and one recovered consciousness 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.

Figure A. Two-year outcomes in VS/UWS patients with non-traumatic brain injury (non-TBI)



Legend: non-TBI, non-traumatic brain injury; MCS-, minimally conscious state minus; VS/UWS, unresponsive wakefulness syndrome

Figure B. Two-year outcomes in VS/UWS patients after TBI (n=9)



Legend: MCS-, minimally conscious state minus. TBI, traumatic brain injury; VS/UWS, unresponsive wakefulness syndrome.



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 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. A 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⁽⁸⁾.



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6

UNEXPECTED EMERGENCE FROM THE VEGETATIVE STATE: DELAYED DISCOVERY RATHER THAN LATE RECOVERY OF CONSCIOUSNESS

Willemijn S. van Erp • Anouk M.L. Aben • Jan C.M. Lavrijsen • Pieter E. Vos • Hans Bor •
Steven Laureys • Raymond T.C.M. Koopmans • Journal of Neurology 2019; 266:3144-3149.



ABSTRACT

Background

The vegetative state, also known as the unresponsive wakefulness syndrome, is one of the worst possible outcomes of acquired brain injury and confronts rehabilitation specialists with various challenges. Emergence to (minimal) consciousness is classically considered unlikely beyond 3–6 months after non-traumatic or 12 months after traumatic etiologies. A growing body of evidence suggests that these timeframes are too narrow, but evidence regarding chances of recovery is still limited.

Objective

To identify the moment of recovery of consciousness in documented cases of late emergence from a vegetative state.

Methods

Four cases of apparent late recovery of consciousness, identified within a prospective cohort study, were studied in-depth by analyzing medical, paramedical and nursing files and interviewing the patients' families about their account of the process of recovery.

Results

All patients were found to have shown signs of consciousness well within the expected time frame (5 weeks – 2 months post-ictus). These behaviors, however, went unnoticed or were misinterpreted, leading to a diagnostic delay of several months to over 5 years. Absence of appropriate diagnostics, the use of erroneous terminology, sedative medication but also patient-related factors such as hydrocephalus, language barriers and performance fluctuations are hypothesized to have contributed to the delay.

Conclusions

Delayed recognition of signs of consciousness in patients in a vegetative state may not only lead to suboptimal clinical care, but also to distorted prognostic figures. Discriminating late recovery from delayed discovery of consciousness therefore is vital to both clinical practice and science.



INTRODUCTION

The vegetative state, also known as the unresponsive wakefulness syndrome (VS/UWS) is one of the worst possible outcomes of acquired brain injury^(1,2). Patients show spontaneous eye opening but no behavioral signs of consciousness. Emergence from VS/UWS is classically considered unlikely beyond 3–6 months after non-traumatic or 12 months after traumatic etiologies⁽³⁾. These timeframes, however, are likely inaccurate^(4,5). The detection of even minimal awareness is of major clinical importance. In contrast to VS/UWS, patients in a minimally conscious state (MCS)⁽⁶⁾ show residual sensory and emotional processing, including nociception^(7,8) and have better chances of further recovery⁽⁵⁾. Behaviorally, MCS is characterized by signs of awareness of the self and/ or the environment without functional communication or functional object use⁽⁶⁾. Based on the absence or presence of evidence for language processing, patients are considered respectively to be in MCS- (showing for example visual pursuit or localization of noxious stimuli) or in MCS+ (showing reactions such as inconsistent command following and intentional communication)⁽⁹⁾.

Differentiating VS/UWS from MCS unfortunately remains challenging, as reflected by a high rate of misdiagnosis⁽¹⁰⁾. In this context of diagnostic and prognostic uncertainty, clinicians and families face vital decisions on treatment goals and limitations.

We present four VS/UWS patients in whom signs of consciousness were identified beyond the aforementioned timeframes and propose clinical and scientific recommendations that arise from their stories.

METHODS

Patients were identified within a cohort of 31 patients in VS/UWS at least 1 month post-ictus, founded in the Netherlands in 2012. On-site assessment of level of consciousness (LoC) by a trained clinical researcher (WvE) consisted, at baseline and at each follow-up, of a single Coma Recovery Scale-revised (CRS-R)⁽¹¹⁾ plus observation of possibly



conscious behavior reported by proxies and staff. Findings, including the diagnostic uncertainty associated with this single assessment, were explicitly communicated with the treating physician. We invited families and staff to contact us between follow-up visits if the patient's reactions changed.

For this case series, we included patients with a CRS-R based VS/UWS diagnosis, in whom the first signs of consciousness were detected during formal follow-up at or after 6 (non-traumatic) or 12 months (traumatic brain injury). Patients' representatives gave written, informed consent. A medical research ethics committee concluded that no complementary review was needed.

Clinical files were searched for descriptions of possibly conscious behavior. We compared proxies' accounts of the course of recovery to the chronology of the formal diagnostic process.

RESULTS

(see table 1; full CRS-R scores available as supplementary material)

Patient 1. A 49-year-old male, non-Dutch speaking, sustained hypoxic brain damage during an out-of-hospital cardiac arrest in 2013. With a diagnosis of 'coma vigil' he was discharged to a regular nursing home, where the physician described his condition as a 'comatose state'. After two research-related CRS-R assessments corresponding to a diagnosis of VS/UWS, during the third examination, 8 months post-ictus, he showed automatic motor behavior. Medical files revealed that in the first 3 months after the incident, the patient manually removed his tracheal cannula twice and tracked visual stimuli with his eyes. The eventual diagnosis of MCS did not change the patient's treatment. Two years and 8 months post-ictus, he remains in MCS-, unable to communicate, immobile, and dependent on others for all activities of daily living.



Patient 2. A 64-year-old female suffered a subarachnoid hemorrhage in 2008 and was transferred to a specialized nursing home without formal LoC diagnosis seven weeks later. Upon admission, the physician concluded she was in a ‘vegetative state’, although she showed ‘some visual tracking’. The patient received valproic acid for epilepsy and increasing doses of midazolam to treat spasticity. Four years and 9 months post-ictus valproic acid was discontinued. Within weeks, the patient’s family noted her smiling in response to names of loved ones. Her diagnosis did not change, however, until the clinical researcher (WvE) identified visual pursuit and automatic motor behavior, corresponding to MCS at 5.5 years post-ictus. Midazolam was discontinued, but no interventions aimed at further recovery took place. At the time of this study, over 7 years post-ictus, the patient inconsistently follows commands (corresponding to MCS+) but is unable to communicate.

Patient 3. A 27-year-old male sustained extensive traumatic brain injury (diffuse axonal injury, acute subdural hemorrhage and traumatic subarachnoid hemorrhage) during a car accident in 2011. Without explicit LoC diagnosis, 5 weeks later he was admitted to a specialized nursing home with a therapy program aimed at recovery of consciousness. Despite the presence of visual pursuit and localization of noxious stimuli, his physician considered him to be in a ‘vegetative state’. When his reaction pattern deteriorated at 5 months after the injury, all paramedic therapies were discontinued. During research assessment only reflexes were seen. Following transfer to a regular nursing home closer to the patient’s home-town, 8 months after the injury, a brain CT-scan made on the family’s request demonstrated an obstructive hydrocephalus. An intraventricular drain was inserted. The patient recovered command following at 12 months, and functional communication at 16 months post-ictus corresponding to a conscious state. Three years on he lives in a supervised apartment. He eats, drinks and mobilizes independently and communicates verbally.

Patient 4. A 61-year-old male with limited Dutch proficiency survived an out-of-hospital cardiac arrest in 2014 in a state characterized by the cardiologist as ‘poor



neurological recovery'. Upon admission to a regular nursing home, his condition was described as a 'comatose state'. Six weeks after the incident the patient was noted to follow objects and people with his eyes; at 2 months post-ictus he showed nuanced facial expressions in relation to emotional context. The first formal CRS-R assessment at 5 months post-ictus by the study researcher elicited reflexes only. The family, despite instructing the patient in his native language, could not provoke conscious behavior either. At 8 month follow-up, the patient demonstrated reproducible automatic behavior consistent with MCS-. He was transferred to a specialized nursing home but showed no further improvement.

Table 1. Overview of case findings

Patient	1	2	3	4
Sex, age at incident	M, 49	F, 64	M, 27	M, 61
Fluency in Dutch	No	Yes	Yes	No
Year of incident, etiology	2013, OHCA	2008, SAH	2011, TBI	2014, OHCA
Diagnosis hospital	'Coma vigil'	'No LoC diagnosis'	'Vegetative state'	'Poor neurological recovery'
Diagnosis nursing home	'Comatose state'	'Vegetative state'	'Vegetative state'	'Comatose state'
Centrally acting medication with sedative side-effects	None	Valproic acid	Baclofen	Levetiracetam and phenytoin
First documented signs of consciousness (time post-ictus, witness)	Patient repeatedly removes tracheal cannula (2 months post-ictus, staff)	Visual pursuit (7 weeks post-ictus, staff)	Visual pursuit, localization of noxious stimuli (5 weeks post-ictus, staff)	Visual pursuit (6 weeks post-ictus, staff)



First formal recognition of signs of consciousness (time post-ictus, assessor)	Automatic motor behavior (10 months post-ictus, clinical researcher)	Visual pursuit and automatic motor behavior (5.5 years post-ictus, clinical researcher)	Functional communication and object use (16 months post-ictus, clinical researcher)	Automatic motor behavior (8 months post-ictus, clinical researcher)
Somatic events prior to recovery	None identified	Discontinuation of valproic acid and midazolam	Treatment of obstructive hydrocephalus	None identified
Outcome (time post-ictus)	MCS, fully dependent (2 years, 8 months post-ictus)	MCS, fully dependent (7 years, 3 months post-ictus)	Conscious, assisted living, 24-hour care. Independent intake of food and drink, verbal communication, mobile (5 years, 4 months)	MCS, fully dependent (1 year, 5 months)

Legend: OHCA = out-of-hospital cardiac arrest, SAH = subarachnoid haemorrhage, TBI = traumatic brain injury

DISCUSSION

On first sight, the stories in this case-series might be regarded as unexpected or ‘miraculous’ recoveries worthy of press attention⁽¹²⁾. On closer inspection, all patients showed signs of consciousness within the established prognostic timeframes. Rather than examples of remarkably late *recovery* of consciousness, these are cases of late *discovery* of consciousness, remarkable nonetheless⁽¹³⁾. Why was these patients’ potential not recognized sooner?

First, there is the apparent absence of standardized behavioral assessment in daily practice, the inaccurate diagnostic terminology and the misinterpretation of conscious behavior. None of the patients’ medical files or transfer letters mentioned validated scales for LoC determination, let alone repeated CRS-R assessments. Only one patient left the hospital with a formal, though outdated, diagnosis (‘coma vigil’). Upon nursing home admission, two patients were incorrectly labeled as being in a ‘comatose state’, and the other two were considered ‘vegetative’ though both showed signs of consciousness. Those behaviors were, by all accounts, noticed but erroneously interpreted as ‘unconscious reflexes’. When patient 3 subsequently stopped showing signs of consciousness, due to, as it turned out later, the development



of hydrocephalus, no expert consultation was sought. Earlier referral for radiological evaluation might have detected this complication sooner.

The second factor concerns the various internal and external influences on patients' performances. Language barriers (patients 1 and 4), sedative drugs (patient 2) and patient 3's hydrocephalus are known diagnostic confounders⁽¹⁴⁻¹⁶⁾, as are fluctuations in arousal and awareness⁽¹⁷⁾. Patient 1, for example, showed only reflexive behavior during assessment while already capable of object manipulation (i.e. removal of his own tracheal cannula) and visual pursuit. Repeated CRS-R measurements might have detected such signs of consciousness earlier. Had it not been for the research project, however, some of the patients' recoveries might have not been discovered at all.

VS/UWS is a diagnosis per exclusionem: absence of proof is not the same as proof of absence. Only if a stimulus is perceived, processed and gives rise to specific motor behavior we know that someone is conscious⁽¹⁸⁾. Both input to and output of conscious brain processing may be hampered, thus masking what the patient is perceiving. The detection and, if possible, treatment of epilepsy, low arousal due to sedatives or metabolic impairments, dysphasia, motor impairment, sensory deficit, neglect, attention fluctuations, hydrocephalus, and compensation of language barriers should be regarded as prerequisites for a diagnosis of VS/UWS. On top of that, a formal diagnosis of VS/UWS or MCS warrants a minimum of 5 standardized clinical assessments at different timepoints within a short time interval (e.g. 14 days)⁽¹⁹⁾.

In view of the low prevalence of disorders of consciousness in general⁽²⁰⁾, and limited specialized care for these conditions even in high-income nations such as the Netherlands⁽¹⁰⁾, it is unreasonable to expect every clinician to be able to discriminate between VS/UWS and MCS. Underestimation of a patient's awareness, however, may lead to erroneous prognostication, therapeutic nihilism, inadequate clinical and pain management and misinformed end-of-life decisions. Delayed recognition of recovery of consciousness, particularly in long-term care, should also be taken into account during the continuing revision of the prognosis of VS/UWS. A recent publication on late



emergence from VS/UWS hypothesized that recovery taking place between formal LoC assessments may go unnoticed⁽²¹⁾. Our case-series proves this to be true. The actual moment of recovery of consciousness can precede its formal recognition by years. Still, this study cannot be seen as proof that late recovery is non-existent.

This study is of modest size and of only partially prospective nature. It is likely that a scientific or clinical context with structural CRS-R based evaluations in place for all patients with prolonged disorders of consciousness would identify late recognition of recovery more often. A mobile team, providing expert-level and evidence based diagnostic assessment on-site and educating care professionals and families, could minimize future misdiagnoses, diagnostic delays and both scientific and public misconceptions about ‘miracle recoveries’. Bringing the expert to the patient, instead of vice versa, takes away the practical challenges of a clinical transfer, as well as the reduced arousal that often becomes apparent after a patient in VS/UWS reaches hospital. Such a relatively simple innovation would bring patients with prolonged disorders of consciousness closer towards the care and attention they deserve.

SUPPLEMENTARY DATA: CRS-R SCORES

PATIENT 1	Hospital discharge	Nursing home admission	Research visit 1	Research visit 2	Research visit 3	Research visit 4
			4 months post-ictus	7 months post-ictus	10 months post-ictus	2 years, 8 months post-ictus
Auditory	No CRS-R	No CRS-R	0	0	0	0
Visual			0	0	0	0
Motor			1	1	5	5
Oromotor/verbal			1	1	2	2
Communication			0	0	0	0
Wakefulness	'Coma vigil'	'Comatose state'	2	2	2	2
Conclusion			VS/UWS	VS/UWS	MCS-	MCS-



PATIENT 2	Hospital discharge	Nursing home admission	Research visit 1 4 years post-ictus	Research visit 2 5 years post-ictus	Research visit 3 5.5 years post-ictus	Research visit 4 7 years post-ictus
Auditory	No CRS-R	No CRS-R	1	0	1	3
Visual			1	1	3	3
Motor			1	1	5	5
Oromotor/ verbal			1	1	2	2
Communi- cation			0	0	0	0
Wakeful-ness			0	2	2	3
Conclusion	No diagnosis	'Vegetative state'	VS/UWS	VS/UWS	MCS-	MCS+

PATIENT 3	Hospital discharge	Nursing home admission	Research visit 1 5 months post-ictus	Research visit 2 16 months post-ictus
Auditory	No CRS-R	No CRS-R	1	4
Visual			1	5
Motor			1	6
Oromotor/ verbal			1	2
Communication			2	2
Wakefulness			2	3
Conclusion	No diagnosis	'Vegetative state'	VS/UWS	Conscious state

PATIENT 4	Hospital discharge	Nursing home admission	Research visit 1 5 months post-ictus	Research visit 2 8 months post-ictus	Research visit 3 1 year 5 months post-ictus
Auditory	No CRS-R	No CRS-R	0	0	0
Visual			0	0	0
Motor			1	5	5
Oromotor/ verbal			1	2	1
Communication			0	0	0
Wakefulness			2	1	2
Conclusion	'Poor neurological recovery'	'Comatose state'	VS/UWS	MCS-	MCS-



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7

GENERAL DISCUSSION



This thesis describes the prevalence and outcomes of the unresponsive wakefulness syndrome (UWS), focusing on level of consciousness, misdiagnosis and the end of life.

The final chapter provides an overview of the main findings, which are then related to what was already known and to the methodological issues that should be taken into account. A fictional case report illustrates two possible outcomes of prolonged disorders of consciousness (PDOC) in a setting of optimal care, which I argue could become reality in the near future. Lastly, recommendations for clinical practice, education, policy, and research are given.

Main findings

- The prevalence of UWS in the Netherlands is 0.1-0.2 institutionalized patients per 100.000 members of the general population;
- This is the lowest UWS prevalence documented worldwide;
- Nowadays, there are no patients below the age of 18 in UWS in Dutch nursing homes, in contrast to the situation in 2003;
- The most common etiology of UWS in the Netherlands is postanoxic encephalopathy following out-of-hospital resuscitation;
- 41% of patients presumed to be in UWS are found to be at least minimally conscious when examined by an experienced assessor using the appropriate behavioral scale;
- 79% of UWS patients received an incorrect level of consciousness diagnosis at hospital discharge, or none at all;
- Up until 2019, it was a rarity for a patient in prolonged UWS to have ever followed specialized rehabilitation;
- If a UWS patient is found to show signs of consciousness unexpectedly late, i.e. beyond 1 year after their injury, it is likely that the actual recovery took place well within the



expected time-frame, but that it went unnoticed or was not recognized as such;

- Patients may survive in UWS for over 3 decades after their brain injury, but many of them die within the first 2 years;
- 50% of deaths in UWS patients follow an elderly care physician's decision to discontinue artificial nutrition and hydration (ANH);
- Even in extremely prolonged UWS, the treating physician can decide to discontinue ANH. This decision tends to be linked to a specific trigger, such as a complication, or a seemingly haphazard event unrelated to the patient's condition;
- Dying after ANH withdrawal in UWS may take up to 18 days and is not invariably experienced as peaceful by those professionally and personally involved.

Discussion of the main findings and methodological considerations

Chapter 2 describes a systematic review of UWS prevalence studies in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁽⁶⁾. The results of this study allowed us to design our ideal prevalence study – one that would involve all health care institutions nationwide, aiming at 100% diagnosis verification by means of the Coma Recovery Scale-Revised (CRS-R).

In April 2012, I carried out a prevalence study accordingly, contacting 367 health institutions and 270 individual physicians within 5 workdays after the point prevalence date and screening 72 patients presumed to be in UWS as fast as logistics would allow. While response rates were high in general, I failed obtaining responses from over 200 physicians for people with intellectual disability; 80% of the total group that was contacted did not respond. This, combined with the fact that we did not target patients being cared for at home, may have contributed to the absence of patients younger than 18 in the population we identified. Nonetheless, at the end of the data acquisition period, it was safe to say that the complete population of UWS patients institutionalized in the Netherlands was now known. With hindsight, it would have been better to have included



these individuals right away into the cohort study which we had already fully prepared. Not wanting to burden physicians and families with a double consent procedure, however, I only asked them for their consent to participate in the cohort study on a second instance, 3 months later. By then, 1 out of every 3 patients had died. Inclusion remained problematic for 6 years. Despite a website, over 30 presentations to a variety of audiences in which I mentioned the study, and the efforts of all the members of our research group, detecting patients with this rare condition, with its high mortality and in a context of disorganized care, was challenging. As an epidemiological study in the classic sense, it therefore has little worth. The small number of inclusions, possible selection bias, variable time post-ictus at baseline, missing data and loss to follow-up did not allow us to calculate survival curves and recovery rates; those would have given a distorted view.

The novelty and relevance of our Dutch cohort results lies in the fact that we were able to prospectively study scenarios at UWS patients' end of life. For as long as people have survived acute brain injuries and are left with PDOC, there has been discussion about the justifiability of prolonging their lives. The first scientific insights into this dilemma came in 1990 and 2005 with three publications arising from Dutch long-term care⁽²⁻⁴⁾. A qualitative study identified three different scenarios in patients in prolonged UWS: continuation of artificial nutrition and hydration (ANH) and treatment of complications and disease; continuation of ANH, but withholding treatment of potentially life-threatening complications and disease; and discontinuation of ANH, a scenario that had been discussed in a single case report in 1990 as well^(2,4). In a retrospective analysis of 43 UWS deaths between 2000 and 2003, withholding treatment for a complication was most often observed, in 24/43 cases (56%). Discontinuation of ANH preceded only 9/43 UWS deaths (21%)⁽³⁾. A decade later, this distribution has shifted: dying after discontinuation of ANH is now the primary scenario of dying in UWS.

Looking into these decisions, we found that the elderly care physicians linked the cessation of ANH to specific events: a complication or a dysfunctional feeding tube, for example. We hypothesized that a decision like this needs the momentum of some sort



of trigger: a factor, change or incident seemingly outside of the family's and physician's influence. The committee of the Royal Dutch Medical Association that wrote about limits to life-prolongation in UWS in 1997 considered such apparently reactive acting 'odd', as it implicitly assumed *'...that the situation of a prolonged comatose [sic] patient usually would not require decision-making, while a - coincidentally occurring - complication [...] apparently would warrant reconsideration of that situation'⁽⁵⁾*. Our study shows that prolonged UWS in itself, despite the inherently increasing prognostic certainty, in itself does not invariably provide enough ground to discontinue ANH.

Another unexpected finding, contradicting the idea that there is a fixed 'window of opportunity' in which decisions to withdraw life-prolonging treatment have been thought to be possible^(6,7) was that in some cases discontinuation of ANH occurred after years, even decades, of UWS.

Deathbeds after ANH withdrawal in UWS have been described, in the aforementioned case studies and a recent qualitative study on family's experiences at the bedside of dying UWS patients, to be 'peaceful' ^(4,8,9). This experience was shared by many physicians in our study, but not invariably so. We found that up to 18 days may pass between the withdrawal of ANH and the patient dying; to the best of our knowledge, such a long period of time has not been described before^(10,11). The emaciation of the patient in some cases was considered to have been burdensome to the patient's family and to staff as well.

The prognosis of UWS is one of the major knowledge gaps at the moment. Following the Multi Society Task Force on the Persistent Vegetative State landmark publication in 1994, emergence from traumatic UWS was expected only to happen within the first 12 months after the causative incident⁽¹²⁾. Non-traumatic UWS-patients were considered to be beyond chances of recovery already at 3-6 months post-ictus^(5,12-14). In recent years, however, a growing body of scientific literature suggests that these timeframes are too pessimistic⁽¹⁵⁾. As stated before, the cohort did not allow us to determine the chances of recovery from UWS in the Netherlands. I did, however, detect signs of consciousness in patients who had been in UWS for years and we wondered whether this reflected actual



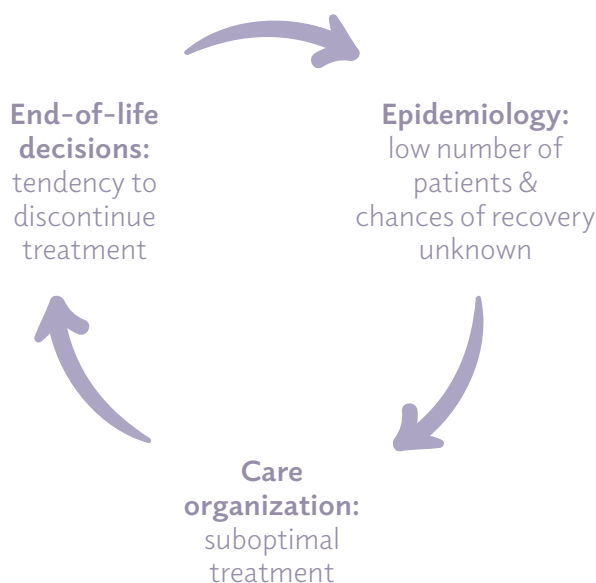
late recovery, contradicting the then accepted prognostic expectations. After reconstructing these patients' recovery patterns with the help of their families, nurses and physicians, we discovered that they had, in fact, all recovered well within those timeframes. Instead of late recovery, these were cases of late *discovery* of consciousness. This phenomenon was introduced first in 2006⁽¹⁶⁾ and hypothesized to be a possible bias in prospective studies on PDOC later⁽¹⁷⁾. We observed it real-time in our cohort. The imperative never to base a level of consciousness diagnosis on a single CRS-R assessment, even when it is performed together with the patient's proxies – has been scientifically backed up since the start of the cohort⁽¹⁸⁾. It is well possible that the prevalence of UWS in the Netherlands in fact is even lower than our results suggest.

Recent developments in PDOC care in the Netherlands

One of our publications on UWS in the Netherlands carries the subtitle 'outcomes from a vicious circle'⁽¹⁹⁾. We argue that epidemiology, suboptimal care and end-of-life decisions can form a downward spiral (figure A). Step 1: the group of patients seems small and recovery is rarely witnessed, especially by those responsible for care in the acute phase. Step 2: because of the supposed small numbers and modest chances of meaningful recovery, care is organized ad-hoc, resulting in misdiagnosis, shattered expertise, lack of specialized rehabilitation and family counselling. Step 3: decisions about whether or not to continue life-supporting treatment are made without solid diagnosis or scientifically sound prognostication, often by a physician without knowledge of the possible long-term outcomes and without a concrete roadmap to adequate post-acute and long-term care. This brings us back to step 1: the number of patients and their chances of recovery remain small due to a tendency to discontinue life-prolonging treatment, while those who survive continue to receive suboptimal care.



Figure A. The vicious circle of unknown epidemiology, suboptimal care and tendency to discontinue treatment in VS/UWS



This thesis shows that even in the Netherlands, with its high standard of living, education and healthcare, patients surviving the most severe acute neurological injuries get caught in such a vicious circle, as well as their families and professional caregivers.

Fortunately, better times lie ahead, or perhaps have already arrived⁽²⁰⁾. With the installation of a national network of expertise dedicated to the severest outcomes of acquired brain injury, called ‘EENnacoma’ (‘one after coma’) in 2016, institutions providing care for UWS, MCS and exit-MCS patients after hospital discharge have been linked to each other, to the patients’ family association, and to academic research (www.eennacoma.net). With high expectations, we look forward to the implementation of the 2018 report ‘Towards more awareness: appropriate care for patients with prolonged disorders of consciousness’, initiated by the Brain Foundation of the Netherlands and the National Healthcare Institute⁽²¹⁾. Written with colleagues from all disciplines involved in



the care for UWS and MCS patients, this shared effort has already caused the infamous age limit for early intensive neurorehabilitation for PDOC to be lifted. And this might just be the beginning. In the next section, I describe a fictional case with two different possible outcomes, set in the optimal context which is now within reach in the Netherlands.

Towards optimal care for PDOC: recommendations for clinical practice and policy

Since January 2019, virtually all patients in the Netherlands with newly acquired prolonged disorders of consciousness receive specialized diagnostics. The one rehabilitation center in the Netherlands that provides specialized rehabilitation for this group, enables me to visit these patients while they are still in hospital to assess their level of consciousness and educate both their families and medical and nursing staff on-site. From here, it is a relatively small step to a multidisciplinary mobile outreaching team of experts providing diagnostic and therapeutic advice wherever and whenever needed. Linked to a specialized clinical diagnostic unit with accessory techniques (fMRI, PET, EEG, MEG), such an innovative service could render the risk of misdiagnosis virtually non-existent. Moreover, the team could provide those surrounding the patient, whether personally or professionally involved, with advice on rehabilitation issues, off-label medication, ethical dilemmas (by facilitating moral deliberations) etcetera along the chain of care. The team could also develop a protocol for PDOC management in the hospital phase, with specific attention to regulation of sensory input, optimization of circadian rhythm, behavioral monitoring, family counselling and decision-making in the absence of prognostic certainty⁽²²⁾.

In addition to the obvious improvement for individual patients, their families and professional caregivers, an outreaching team of experts operating beyond bureaucratic borders is an important step towards centralizing care on a national scale for this small and complex group.

A recent report on how specialist knowledge and specialized care can be made available to those who need them, commissioned by the Dutch ministry of Health, proposes a framework of dedicated centers of expertise linked to one knowledge center⁽²³⁾. For



PROLONGED DISORDERS OF CONSCIOUSNESS IN 2022: TWO OUTCOMES IN A CONTEXT OF OPTIMAL CARE

A 41-year old female sustains severe brain damage during an out-of-hospital cardiac arrest. Her initial prognostic test results are inconclusive and the medical staff after consultation with the family decides to observe her clinical development for at least 5 days after the discontinuation of sedation. She opens her eyes on day 5 post-ictus and shows sustained periods of wakefulness, but no command following.

The outreaching PDOC-team is consulted and one of the experts visits the patient on site 10 days post-ictus. After discussing the latest medical developments with the patient's treating physician, identifying factors possibly hindering the patient's performance (subclinical epilepsy, sedative medication, etc.) and staff and family's accounts of behavior possibly indicative of consciousness, she performs a CRS-R enhanced with personalized stimuli (e.g. the patient's partner calling her name for the auditive subscale).

Outcome 1

The patient shows startle reflexes on visual and auditory stimulation, abnormal posturing in reaction to a noxious stimulus, oral reflexes, and no communication. Her eyes are open spontaneously throughout the assessment. There are no signs possibly indicative of discomfort. According to the family, the patient relaxes when they speak to her. She seems to look right through them, does not respond to commands and shows no affective reactions. The patient does not cooperate when the nurses wash or dress her. She doesn't fumble with sheets or tubes.



The consultant provides the family with general information about disorders of consciousness. The patient-specific findings, however, are only discussed with the treating physician in order not to interfere with the treating relationship. The consultant explains to the treating physician that the history, input from staff and family, and a single CRS-R point towards a diagnosis of UWS, but that this diagnosis requires at least 5 assessments. However, a best- and worst-case scenario can be outlined. In the most positive evolution of events, the patient will regain minimal signs of consciousness and eventually emerge to a conscious state. In this scenario, it is likely that she will have considerable cognitive and motor impairments, although it is certainly not impossible for her to be happy.

On the other side of the spectrum of possible outcomes, the patient is confirmed to be in UWS and remains unresponsive, in which case the treating physician, most likely in long-term care, will eventually discontinue life-prolonging treatment once chances of meaningful recovery have passed.

The treating physician discusses the consultant's conclusions with the patient's family. The patient, a medical doctor with a PhD and two young children, is described as a particularly autonomous, active and independent. Her family is sure that she would not have given consent for any treatment that would, at best, have her reach a state in which she would not be able to think and act as she could before.

After moral deliberation, led by one of the ethicists from the outreaching PDOC-team, the treating physician discontinues artificial nutrition and hydration and starts symptomatic treatment. The patient's family receives continuous support by a psychologist, a social worker and a spiritual counsellor, who are also available to the professional caregivers. The patient dies after 7 days, in the presence of her partner.



Outcome 2

The patient shows visual pursuit and localization of her own name when called by her husband. There is flexion withdrawal in reaction to a noxious stimulus, oral reflex behavior, and no communication. Her eyes are open spontaneously throughout the assessment. There are no signs possibly indicative of discomfort. According to the family, the patient looks them in the eye and she has cried once when her children cuddled her. Her nurses tell the consultant the patient seems to move her arms in the right direction when they dress her. She sometimes fumbles with her PEG-tube. The consultant provides the family with general information about disorders of consciousness. The patient-specific findings, however, are only discussed with the treating physician in order not to interfere with the treating relationship. The consultant explains to the treating physician that the history, input from staff and family, and a single CRS-R show that the patient is at least in MCS-, and that the presence of language function cannot be ruled out at this stage. In the most positive evolution of events, the patient will eventually emerge to a conscious state. In this scenario, it is likely that she will have considerable cognitive and motor impairments, although it is certainly not impossible for her to be happy.

On the other side of the spectrum of possible outcomes, the patient remains minimally conscious without regaining the capacity of functional communication.

The treating physician discusses the consultant's conclusions with the patient's family. The patient, a medical doctor with a PhD and two young children, is described as a religious person who saw value and meaning even in suffering. Her family is sure she would have wanted to be helped to recover, regardless of the outcome, and that she would have considered even life in MCS- to be worthwhile. They understand, however, that the responsibility for starting or continuing any medical treatment lies with the treating physician.



The patient is referred to the early intensive neurorehabilitation unit and completes 14 weeks of multimodal interventions aimed at recovery of consciousness and somatic optimization. Her family receives intensive counselling from a psychologist and a social worker – a prerequisite for the patient’s participation. At the end of the program, the patient is in MCS+ with inconsistent command following and intentional communication, and is transferred to a prolonged intensive neurorehabilitation unit in a specialized nursing homes closer to her home town. She continues to receive intensive multidisciplinary therapy and routine CRS-R assessments, while her family is offered psychological, social and spiritual counsel. At 10 months post-ictus, the patient regains the ability to functionally communicate. Neuropsychological evaluations reveal impairments in executive and memory functions, and the patient is admitted to a cognitive neurorehabilitation program in a regular clinical rehabilitation center. At 15 months post-ictus, she is discharged to an assisted living facility specialized in patients with acquired brain injury. She mobilizes independently in an electronic wheelchair, has independent oral intake and requires the help of one person in other activities of daily living. She describes her quality of life as ‘very good’.



EENnacoma to become a knowledge center would require, amongst other criteria, for it to be closely linked to educational institutes (from university to in-service education), to coordinate research, to collaborate with patient organizations, to develop guidelines and implement them and to produce competence profiles. The foundations of these roles have been laid in the past 3 years, and could be strengthened and expanded by establishing stronger ties to academic networks in the field of acute, post-acute and long-term care.

EENnacoma should promote optimal, academically-based care for PDOC-patients through the following partners c.q. centers of expertise (which may combine roles):

- A team of researchers;
- An outreaching, mobile team of experts;
- One or two specialized clinical diagnostic units within an academic medical center;
- A specialized rehabilitation center for early intensive neurorehabilitation;
- Circa 6 specialized nursing homes providing prolonged intensive neurorehabilitation;
- Circa 15 specialized nursing homes providing chronic care for patients with PDOC and for patients who have regained consciousness with severe cognitive and motor impairments;
- A clinical unit specialized in cognitive neurology and neuropsychiatry providing brief, intensive in-patient programs to diagnose and treat neuropsychiatric symptoms after acquired brain injury for patients who have regained consciousness.



In PDOC, the first 24 months post-ictus are critical. This is the timeframe in which recovery takes place, and the foundations for a new life, which may be different but can certainly be worthwhile, can be laid. After the early intensive neurorehabilitation phase, patients who have not regained consciousness remain in need of specialized, intensive care and expertise. A care protocol for prolonged intensive neurorehabilitation, written by members of EENnacoma, is already underway and four nursing homes throughout the country have committed themselves to it. It is likely that the devastatingly low numbers of UWS patients receiving specialized treatment we found in our studies, will be a thing of the past very soon.

The first 24 months after severe acquired brain injury also encompass the time in which reasonable certainty about the patient's prognosis is reached, and in which absence of (further) recovery must be faced. The fact that to this day, some UWS patients in the Netherlands receive life-prolonging treatment for years, even decades beyond chances of recovery of consciousness, testifies of the complexity of these confrontations. We know that moral deliberations can help dissolve such status quo⁽²⁴⁾, and our finding that the possibility of discontinuation of ANH exists even in extremely prolonged UWS is encouraging. The window of opportunity for letting someone in such a hopeless state go, apparently never fully closes. At the same time, knowing this puts extra weight on the shoulders of physicians taking on the responsibility of caring for patients in prolonged UWS. Even after years, the question 'is this what my patient would consent to?' cannot be left unanswered, and the answer cannot be left without action.

Lastly, with respect to optimal care after discontinuation of ANH in UWS patients, this thesis shows that physicians should be set for intensive palliative care during a period of up to three weeks, and prepare their colleagues and most importantly the patient's family for the same. Because of PDOC patients' limited abilities to communicate pain and discomfort, it seems appropriate to administer symptomatic treatment even in the absence of objective signs of distress.



Implications for education

The adverse effects of cardiopulmonary resuscitation (CPR), which may be carried out by non-professional bystanders, are relatively underexposed in scientific and lay-man's publications. Our studies show that when it comes to CPR, there is harm in trying: 1 in 3 UWS patients is in that state after a 'successful' resuscitation. Next to the possibility of the patient dying despite CPR, and the smaller (but of course very relevant and ever increasing) chance of full recovery, there is a third scenario in which the heart resumes its function while the brain does not or in a severely damaged state. Our findings warrant an explicit disclosure to be added to every single resuscitation course, regardless of whether the participants are health care professionals or dedicated non-medics.

Medical students should be familiarized with the many shades of grey in the outcome of acquired brain injury, including patients reporting high quality of life despite severe disabilities, patients with PDOC, and neuropsychiatric symptoms in patients with otherwise 'good' outcome characteristics.

The Netherlands are blessed with an academic medical specialty dedicated to long-term care, which exists nowhere else in the world⁽²⁵⁾. Despite being called 'elderly care physicians', these medical doctors are equipped with all knowledge, competency and skill needed to provide suitable care for patients with complex disease and disorders beyond hospital doors, regardless of age, and with an emphasis on quality of life and patient-centered decision-making. A qualification in complex neurology would greatly enhance their possibilities, not only to the benefit of the relatively small, and in the future more centralized, group of patients with PDOC, but for patients with different sequelae of acquired brain injury, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease and various other neurological conditions resulting in a need for prolonged medical care as well. For Huntington's disease and dementia in younger patients, such qualification possibilities for elderly care physicians already exist^(26,27).

Physicians and other health care professionals taking on the unique responsibility of providing care to patients in UWS and related conditions deserve to be facilitated in



reaching even more specific competencies. EENnacom has written a competence profile for physicians providing both early and long-term intensive neurorehabilitation for PDOC. Interprofessional rotations in neurology, rehabilitation medicine, elderly care medicine (previously known as ‘nursing home medicine’) and clinical research would allow physicians to prepare for and keep up with the quickly evolving PDOC practice.

Implications for research

A 2018 review by the American Association of Neurology characterized the evidence about UWS and MCS prognosis as ‘limited’⁽¹⁵⁾. Despite our efforts, this thesis will not change that status. However, in the near future, the Netherlands might just be the ideal context for studying prolonged disorders of consciousness. Already, identifying new patients is greatly facilitated by the central position of a single rehabilitation center providing early intensive neurorehabilitation regardless of age or etiology. Following up these patients will be easier, as the majority of those who remain in UWS or MCS are subsequently admitted to one of the specialized nursing homes within EENnacom. Patients with prolonged disorders of consciousness being cared for at home could be visited at regular intervals by the outreaching team. The unique benefits and challenges of their situation, with the general practitioner being the treating physician, certainly are worth looking into.

At the other end of the spectrum, I recommend epidemiological studies on UWS and MCS to begin as soon as a patient with an acute, serious brain injury does not regain consciousness after he or she emerges from a coma. It is only by documenting the hyperacute phase that we can eventually optimize decision-making all along the chain of care for patients with the most severe brain damage. A recent study in a large Dutch intensive care unit about outcomes in severe traumatic brain injury, observed that 82% of brain injured patients with who died did so after a decision to withdraw life-sustaining treatment. None of the survivors left the ward with a prolonged disorder of consciousness⁽²⁸⁾. The authors pointed out the tendency to discontinue life-support in patients with the severest brain injuries early after admittance, if no ‘decent outcome’



was expected. But considering the prognostic uncertainty in prolonged disorders of consciousness alone, such predictions lack scientific back-up. It is time to face the fact that doctors cannot – yet – accurately predict the outcome of patients with severe acquired brain injury, and to stop letting that uncertainty transform to therapeutic nihilism and hasty discontinuation of life-sustaining treatment in the acute stages after the injury.

The first quantitative insights into scenarios at the end of life of patients in UWS presented in this thesis of course call for in-depth mixed methods studies. It would be very interesting to carry out a prospective qualitative study with serial interviews with family, physicians, nurses and paramedical staff to see what influences these complex processes and how they are experienced. Quality of dying in patients with prolonged disorders of consciousness is another topic that warrants qualitative research methods in order to optimize the final days of patients in the future.

Concluding remarks and future objectives

Prolonged disorders of consciousness are a result of medical progress. As a consequence, researchers, clinicians and society share a special obligation to the patients and families affected by these conditions. This group of people in particular should be able to rely on tailor-made care, in accordance with the individual patient's presumed wishes and the latest scientific evidence. This thesis testifies of the challenges of providing such tailor-made care for UWS. And timely so, in view of the current momentum in the Netherlands: patients with prolonged disorders of consciousness seem to finally receive the clinical, scientific and societal attention they deserve.

Standing at the verge of these exciting developments, there is no excuse for exclusivity or exclusion. We should strive for the most inclusive collaborations, connecting neuroscience to nursing homes, rehabilitation centers to ICUs, researchers to clinicians, and all of those to (ex-)patients and their families. By studying clinical, neurophysiologic and ethical topics from the moment a patient does not regain consciousness well into the long-term phase, we will ultimately be able to predict who will, and who will not, recover to a state he or she would find acceptable. It will never be easy to be the physician to act



according to those insights; facilitating recovery when possible, and providing palliative care when it is not. With regards to both ends of the spectrum of appropriate care for UWS and MCS patients, no minor tasks lie ahead.

However, based on what I have learned since the beginning of this PhD project in 2011, there do not seem to be insurmountable obstacles either, as long as these tasks are taken on by all parties that share the responsibility for these patients and their proxies.

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8

SUMMARY



Chapter 1. Introduction

The unresponsive wakefulness syndrome (UWS), formerly known as ‘vegetative state’, is one of the worst possible outcomes of acquired brain injury. A patient in UWS opens his or her eyes spontaneously and breathes independently, but shows only reflexive responses to the outside world. The fact that people can survive in such a condition is a relatively new phenomenon and may be regarded as the downside of medical progress. It was not before the 1950s that increasing chances of survival after traumatic brain injury, cardiac arrest and cerebral haemorrhage started to yield not only good outcomes, but also survival without any sign of the patient being aware of their own body or the environment.

From the 1990s onwards, science took on a quest to find out what was going on in the minds of unresponsive patients. Their population turned out to be more heterogeneous than expected; some patients were found to maintain cerebral activity that indicative of conscious processing, although this did not lead to functional communication or functional object use. In a minimally conscious state, patients are able to experience pain and they have better chances of recovery than those in UWS. But despite promising diagnostic innovations such as fMRI, a gold standard for determining one’s level of consciousness has yet to be developed.

Meanwhile in daily practice, physicians providing care for UWS and MCS patients carry a tremendous responsibility. Especially in long-term care, these patients stand out: they are younger than the average nursing home population but require most intensive care and treatment. And anyone who has ever been confronted with UWS, knows that Sleeping Beauty scenarios could not be further from reality.

Much of what is known about that reality, however, comes from a steady stream of scientific publications arising from Dutch nursing homes. It started in 1990, in the midst of a heated public debate about the question whether Ineke Stinissen, a young woman who had been unresponsive for years after an anesthesia error during caesarean section, should be allowed to die. A scientific publication about a similar case, in which an elderly



care physician ultimately decided to withdraw artificial nutrition and hydration (ANH), eventually led to reports from the Health Council (1994) and the Royal Dutch Medical Association (1997). These reports stated, respectively, that cessation of ANH in a hopeless unresponsive state was justified and that the continuation of ANH in such a situation was not. These explicit statements brought the responsibility for the decision to continue or discontinue ANH in UWS from the courtroom back to the clinic.

Although this made the boundaries of treatment of UWS patients clear, the treatment in itself would remain suboptimal for at least two decades. Specialized rehabilitation for prolonged disorders of consciousness was only accessible to patients under the age of 25, and formally did not even qualify as clinical rehabilitation. In the meantime, long-term care developed into a high-quality and increasingly academized sector with specifically trained physicians. Despite a lack of structural funding, various care facilities developed specialized care programs for patients with prolonged disorders of consciousness (PDOC) and carried out scientific research.

Despite these efforts and the ever-increasing understanding of the neurophysiological substrate of consciousness, scientific knowledge about basic characteristics of UWS remains poor. For example, the number of people with this dramatic condition is largely unknown, as is its long-term course.

This dissertation sheds some light on these topics, specifically in relation to the ongoing international debate about the status of life-sustaining treatment for UWS patients. What is the prevalence of UWS, internationally and in the Netherlands? What is its long-term course? How do patients recover, and if they die, how does that happen? And how can we translate this knowledge into more appropriate care?

Thanks to the SBOH, I was given the opportunity in 2011 to combine scientific research with a specialization in elderly care medicine (formerly known as nursing home medicine). This way, the research project developed in a constant exchange between science,



education and practice.

Chapter 2. A systematic literature review of UWS prevalence studies

First, we systematically investigated available UWS prevalence figures in the international scientific literature. Medline, Embase, the Cochrane Library, CINAHL and PsycINFO were searched for cross-sectional point or period prevalence studies on UWS due to acute causes, within the general population. So-called grey data such as government reports were also added. Out of 1032 articles, 14 met the inclusion criteria. Prevalence figures varied from 0.2 to 6.1 patients per 100 000 inhabitants; Lombardy in Italy had 30 times more patients than the Netherlands. But the differences in methodological quality were just as striking as those in prevalence. Our conclusion was, therefore, that no reliable prevalence figures for UWS were available in the international literature.

Chapter 3. A UWS prevalence study

Subsequently, in the spring of 2012, we conducted a nationwide point UWS prevalence study, aiming to identify all institutionalized patients with 100% diagnosis verification using the Coma Recovery Scale-Revised (CRS-R). The response from hospitals, rehabilitation centers and nursing homes was very good (96–100%), but only 52 of the 270 members of the professional association of doctors for people with intellectual disabilities (20%) responded. A total of 72 patients were reported who, according to their treating physician, were in UWS. Signs of consciousness were nevertheless detected with the CRS-R in 41% of these patients; they were in a minimally conscious state or even capable of functional communication or functional object use.

Twenty-four patients only showed reflex behavior compatible with UWS, and the diagnoses of another 9 patients could not be verified because of non-consent (in 7 cases) or recovery between the point prevalence date and the visit to the ward (in 2 cases). This led to a prevalence of 24–33 institutionalized patients who were in UWS for at least 1 month after an acute brain injury, or 0.1 to 0.2 patients per 100 000 members of the general population. The patients were 27–73 years old and had been in UWS for



an average of 5 years. Twelve of the 24 were in UWS after ‘successful’ resuscitation, and in 7 of them the circulatory arrest had been the result of a cardiac event. 83% of the patients were in nursing homes. Some patients who were already far beyond chances of recovering consciousness (up to 25 years after the injury) still had a very active treatment policy, in various cases even including resuscitation.

Chapter 4. Comparison with previous studies

After these results had been published, we reflected on the Dutch perspectives on UWS in a paper in the Dutch Journal of Medicine. A UWS prevalence study had also been done in the Netherlands in 2003, and despite methodological differences (at that time only 9.4% of diagnoses were verified, and only nursing homes were involved), we were able to compare the historic results to those that came out of our new study and discuss the state of affairs in daily practice.

Chapter 5. A UWS cohort study

Shortly after the prevalence study in 2012, we started inclusion in an observational cohort on UWS. Level of consciousness, clinical characteristics, aspects of care and dying scenarios were observed for a total of 6 years. As an epidemiological study, this project failed; the inclusion was problematic due to high mortality and fragmented care, and sometimes I lost sight of patients even after years of follow-up. Nevertheless, we collected data on 31 patients in UWS and were able to draw relevant conclusions on the course of the condition after hospital discharge.

Patients were on average 41 years old when the brain injury occurred. As in the prevalence study, postanoxic encephalopathy following cardiocirculatory arrest, was the main cause of UWS.

Only one patient had had access to specialized medical rehabilitation in the Netherlands. In 79% of cases, the hospital discharge letter mentioned an incorrect level of



consciousness diagnosis – or none at all.

Eighteen of the 31 patients died during the course of the study, and half of those deaths were preceded by an elderly care physician's decision to discontinue ANH. Between 2000 and 2003, death after cessation of ANH had been the dying scenario in only 21% of UWS patients' deaths. Within the new cohort, the decision to discontinue ANH could always be traced back to a specific trigger: a new complication for example, but also a dysfunctional PEG-system. In apparent contradiction with the 'window of opportunity', a critical period in which treatment decisions can be made, in some cases ANH was withdrawn even after decades in UWS.

The death bed after cessation of ANH was generally described as 'calm', but in certain cases, according to the treating physician, the family suffered from the patient's 'emaciation' (doctor's quote). In some patients, over 10 days went by between the cessation of the ANH and the patient dying. At least 3 doctors were asked by their patient's family to euthanize the patient – these requests were, in accordance with applicable regulations, not granted.

We argued, following the example of prof. mr. Eugene Sutorius, that doctors in the Netherlands can only start or continue medical treatment if this treatment meets the professional standard and if the patient consents to it. While the international discussion about life-sustaining treatment in UWS often evolves around arguments for the discontinuation of ANH, Dutch doctors face a reverse burden of proof. The physician must ensure that the treatment they intend to start or continue is medically appropriate and that his or her patient agrees with it. Both criteria are difficult to meet when a patient is in UWS. As mentioned, the Royal Dutch Medical Association stated in 1997 that continuation of ANH in UWS without chance of recovery could not be justified. However, there are now strong indications that the prognostic limits used at the time were too pessimistic. Moreover, the Netherlands has not sufficiently facilitated patients and their relatives in the recovery process for decades. There is a 41% misdiagnosis rate



and specialized rehabilitation was inaccessible to patients over 25 years of age. On top of this, reconstructing the patient's presumed wish about the treatment in question is also problematic in itself.

We demonstrated all of these factors created a vicious circle. Step 1: there are few patients in UWS, and their chances of recovery are unclear. Step 2: care is organized ad hoc and on insufficient scientific grounds, which leads to misdiagnosis, therapeutic nihilism and incomplete information to the patient's family. Step 3: the lack of appropriate care and necessary expertise leads to a tendency to prematurely discontinue treatment. This brings us back to step 1: there are few patients in UWS.

We concluded the article by emphasizing that it is a great merit that in the Netherlands, vital decisions about these vulnerable patients can be made in the clinic, and not in court. However, this professional autonomy can only be sustainable if the patient's potential for recovery can also be optimally explored.

Chapter 6. Late recovery or late discovery of consciousness

During the cohort study, in four UWS patients signs of consciousness were detected unexpectedly late. We wondered whether these cases reflected the idea that the established prognostic timeframes for UWS are too pessimistic. After thorough investigation of the medical and nursing files, and listening to the patients' families' accounts of the course of recovery, we concluded that in all instances recovery took place well within the expected period. These important changes, however, went unnoticed or were misinterpreted, resulting in significant diagnostic delay.

Chapter 7. Discussion

In the general discussion, the key findings of the dissertation are summarized, and we look to the future. At the time of the intended completion of this PhD project, there are numerous promising societal and scientific developments that could lead to a rapid improvement of the situation of UWS patients in the Netherlands and their families.



In 2016, network of expertise ‘EENnacoma’ was established with the aim of facilitating scientifically based, patient-centered care for people with a PDOC and other sequelae of severe acquired brain injury. The report ‘Towards More Awareness: Appropriate Care for People with PDOC’, written by members of EENnacoma in collaboration with the Brain Foundation of the Netherlands in 2018, is in fact a blueprint for precisely such care and has already resulted in the infamous age limit for specialized Early Intensive Neurorehabilitation being lifted. A start has been made with centralized diagnostics; level of consciousness is now evaluated in-hospital on a national scale for every PDOC patient by means of the CRS-R. Thanks to an implementation grant from the Brain Foundation of the Netherlands, a mobile outreaching team of experts will be developed over the next two years, linked to new accessory diagnostic possibilities and a national registry. Moreover, a report from the Dutch Ministry of Health on centers of expertise in long-term care offers guidance in further development of EENnacoma into a nationwide, academic network.

With regard to education, the first recommendation is to add a disclosure to CPR training, so that every healthcare professional and/ or layperson capable of performing this invasive procedure in the future will know there is harm in trying. Medical students should come into contact with the various outcomes of serious non-congenital brain injury during their university training. Despite the name of the specialty, elderly care physicians are well equipped to provide complete, patient-centered and sustainable care to young patients with complex neurological disorders, but deserve the opportunity to pursue special competencies in this area. EENnacoma has already drawn up a competence profile for elderly care physicians and physiatrists who provide care to PDOC patients specifically.

With regard to research, the Netherlands may be regarded as the ideal context for PDOC studies, both for epidemiological research starting in the hyperacute phase and for qualitative research investigating decision-making and dying in PDOC.



The dissertation concludes with the recommendation to work in close collaboration, bypassing the artificial barriers between medical disciplines, between hospitals, rehabilitation centers and nursing homes, and between practice and science, in providing the most scientifically sound and personalized care for people with prolonged disorders of consciousness.





9

SAMENVATTING



Hoofdstuk 1. Inleiding

Het niet-responsief waaksyndroom (NWS), vroeger bekend als ‘vegetatieve toestand’, is één van de slechtst mogelijke uitkomsten van niet-aangeboren hersenletsel die met het leven verenigbaar zijn. Een patiënt in NWS opent de ogen spontaan en ademt zelfstandig, maar laat alleen reflexmatige reacties op de buitenwereld zien. Dat mensen in zo’n ernstig aangedane toestand in leven kunnen blijven is een relatief nieuw fenomeen, en kan beschouwd worden als de keerzijde van de medische vooruitgang. Met de stijgende overlevingskansen na traumatisch hersenletsel, hartstilstand en ernstige hersenbloedingen is de afgelopen 50 jaar ook het scenario ontstaan dat iemand wel in leven blijft, maar geen enkel teken van besef van het eigen lichaam en van de omgeving meer vertoont.

De wetenschap probeerde vanaf de jaren 1990 te achterhalen wat er in de hersenen van hyporesponsieve patiënten omging. De populatie bleek heterogener dan gedacht; een deel van de patiënten vertoonde wel degelijk hersenactiviteit die blijk gaf van enige bewuste gewaarwording, al leidde dat niet tot functionele communicatie of functioneel gebruik van voorwerpen. Dit beeld wordt ‘minimaal bewuste toestand’ genoemd. Minimaal bewuste patiënten blijken onder meer in staat tot het ervaren van pijn en ze hebben betere herstelkansen dan mensen in NWS. Maar ondanks veelbelovende scantechnieken, zoals fMRI, bestaat er nog altijd geen gouden standaard voor het vaststellen van iemands bewustzijnsniveau.

In de dagelijkse praktijk, die zich grotendeels buiten het ziekenhuis afspeelt, dragen de artsen van patiënten in NWS en MCS ondertussen een grote verantwoordelijkheid. Ontwaken zoals Doornroosje is er niet bij, zoals specialist ouderengeneeskunde en filosoof Bert Keizer in 2012 al schreef. Over de realiteit is vanuit de langdurige zorg in Nederland een gestage stroom wetenschappelijke publicaties verschenen. De oorsprong van die traditie ligt in 1990, toen een verhit maatschappelijk debat werd gevoerd over de vraag of Ineke Stinissen, een jonge vrouw die na een anesthesiefout tijdens een keizersnede al jaren niet-responsief was, mocht overlijden. De publicatie van



een vergelijkbare casus, waarin de specialist ouderengeneeskunde uiteindelijk besloot de kunstmatige voeding- en vochttoediening (KVV) te staken, leidde tot rapporten van de Gezondheidsraad (1994) en de KNMG (1997). In die documenten werd gesteld dat, respectievelijk, het staken van KVV in een uitzichtloze bewusteloze toestand geoorloofd was en dat het continueren van KVV in zo'n geval dat juist *niet* was. Daarmee kwam de verantwoordelijkheid voor die beslissing vanuit de rechtszaal terug naar de klinische werkvloer.

Hoewel de grenzen aan de behandeling van patiënten in NWS hiermee helder waren, zou die behandeling zelf nog zeker twee decennia suboptimaal blijven. Gespecialiseerde revalidatie voor langdurige bewustzijnsstoornissen was alleen toegankelijk voor patiënten jonger dan 25 jaar, en gold formeel niet eens als medisch-specialistische revalidatie. Ondertussen ontwikkelde de langdurige zorg zich tot een hoogwaardige en in toenemende mate geacademiseerde sector, met gespecialiseerde artsen als hoofdbehandelaars. Ondanks het ontbreken van structurele financiering ontstonden hier verschillende gespecialiseerde instellingen, waar zo passend mogelijke zorg werd aangeboden en ook wetenschappelijk onderzoek werd verricht.

Ondanks deze inspanningen en het toenemende inzicht in het neurofysiologische substraat van het bewustzijn, bleef de wetenschappelijke kennis over basale kenmerken van NWS pover. Hoeveel mensen er in deze dramatische toestand verkeren bijvoorbeeld is onbekend, net als het antwoord op de vraag hoe het patiënten op de lange termijn vergaat.

Dit proefschrift is bedoeld om hierin nieuwe feiten aan te dragen, zeker ook in relatie tot het internationaal steeds terugkerende debat over het al dan niet continueren van de levensverlengende behandeling bij patiënten in NWS. Wat is de prevalentie van NWS, internationaal en in Nederland? Wat is het beloop? Hoe verloopt het herstel, en als patiënten overlijden, hoe gebeurt dat dan? En hoe kunnen we deze kennis vertalen naar beter passende zorg?



Met dank aan de Stichting Beroepsopleiding Huisartsen werd ik in 2011 in de gelegenheid gesteld het onderzoek te combineren met de opleiding tot specialist ouderengeneeskunde. Zo kon het project tot stand komen in een voortdurende uitwisseling tussen wetenschap, opleiding en praktijk.

Hoofdstuk 2. Een systematisch literatuuronderzoek naar de prevalentie van NWS

Om te beginnen hebben we op een systematische manier onderzocht welke prevalentiecijfers er over NWS in omloop zijn in de internationale literatuur. We zochten in Medline, Embase, the Cochrane Library, CINAHL en PsycINFO naar cross-sectionele punt- of periodeprevalentiestudies over NWS door acute oorzaken in de algemene populatie. Ook zogeheten ‘grijze data’ zoals overheidsrapporten werden toegevoegd. Uit 1032 artikelen kwamen er 14 die aan de inclusiecriteria voldeden. De prevalentiecijfers varieerden van 0.2 tot 6.1 patiënten per 100.000 inwoners; Lombardije in Italië telde 30x meer patiënten dan Nederland. Maar de grote verschillen in methodologische kwaliteit vielen even zeer op als die in prevalentie. Onze conclusie was dan ook, dat er in feite geen betrouwbare prevalentiecijfers voor NWS beschikbaar waren in de internationale literatuur.

Hoofdstuk 3. Een prevalentiestudie naar NWS

Vervolgens voerden we, in het voorjaar van 2012, zelf een landelijke puntprevalentiestudie naar NWS uit, waarbij we streefden naar het identificeren van alle geïnstitutionaliseerde patiënten en naar 100% diagnoseverificatie met behulp van de Coma Recovery Scale-Revised (CRS-R). De respons uit ziekenhuizen, revalidatiecentra en verpleeghuizen was heel goed (96-100%) maar van de 270 leden van de beroepsvereniging van artsen voor mensen met een verstandelijke beperking reageerden er maar 52 (20%). Er werden in totaal 72 patiënten gemeld die volgens hun behandelend arts in een niet-responsief waaksyndroom verkeerden. Bij 41% van deze patiënten werden met de CRS-R toch tekenen van bewustzijn geobserveerd; zij verkeerden in een minimaal bewuste toestand of waren zelfs in staat tot functionele communicatie of functioneel gebruik van voorwerpen.



Vierentwintig patiënten lieten uitsluitend reflexmatige reacties zien, passend bij de diagnose NWS, en bij nog eens 9 mensen kon geen verificatie plaatsvinden vanwege het uitblijven van consent (in 7 gevallen) of herstel tussen de puntprevalentiedatum en mijn bezoek aan de afdeling (in 2 gevallen). Dit leidde tot een prevalentie van 24-33 geïnstitutionaliseerde patiënten die minstens 1 maand na een acuut hersenletsel in NWS verkeerden, oftewel 0.1 tot 0.2 patiënten per 100.000 leden van de algemene populatie. De patiënten waren 27-73 jaar oud en verkeerden gemiddeld 5 jaar in NWS. Twaalf van de 24 waren in NWS na een 'succesvolle' reanimatie, waarbij in 7 gevallen de circulatiestilstand het gevolg was van een cardiaal event. 83% van de patiënten bevond zich in het verpleeghuis. Bij meerdere patiënten die zich al ver voorbij kans op herstel van bewustzijn bevonden (tot 25 jaar na het letsel) gold nog een zeer actief behandelbeleid, soms zelfs inclusief reanimatie.

Hoofdstuk 4. Vergelijking met eerder onderzoek

Nadat deze resultaten in JAMDA waren gepubliceerd, vergeleken we ze in een beschouwend artikel in het Nederlands Tijdschrift voor Geneeskunde met eerder onderzoek. In 2003 was er namelijk ook een prevalentiestudie naar NWS gedaan in Nederland, en ondanks de methodologische verschillen (toen werd slechts 9.4% van de diagnoses geverifieerd, en waren alleen verpleeghuizen betrokken) stelde ons dat in staat het perspectief van patiënten in NWS in Nederland te beschrijven.

Hoofdstuk 5. Een cohortonderzoek naar NWS

Kort na de prevalentiestudie in 2012 startte een dynamische, observationele cohortstudie waarin in principe iedere patiënt in NWS kon worden geïncludeerd. Bewustzijnsniveau, klinische karakteristieken, zorgaspecten en overlijdensscenario's werden gedurende in totaal 6 jaar in kaart gebracht. Als epidemiologische studie bleef dit onderzoek in gebreke; de inclusie was problematisch door de hoge mortaliteit en gefragmenteerde zorg, en soms verloor ik patiënten na jarenlange follow-up alsnog uit het oog. Niettemin verzamelden we data over 31 patiënten in NWS, waaruit relevante conclusies te trekken bleken.



De patiënten waren gemiddeld 41 jaar bij het ontstaan van het hersenletsel. Net als in de prevalentiestudie was postanoxische encefalopathie, ontstaan tijdens een circulatiestilstand, de belangrijkste oorzaak van NWS.

Slechts één patiënt kreeg toegang tot medisch-specialistische revalidatie in Nederland. Bij 79% van de patiënten stond geen of een onjuiste bewustzijnsdiagnose in de ontslagbrief van het ziekenhuis.

Achttien van de 31 patiënten overleden tijdens de looptijd van het onderzoek, en in de helft van die gevallen werd het overlijden voorafgegaan door de beslissing van een specialist ouderengeneeskunde om de kunstmatige voeding- en vochttoediening te staken. Overlijden na staken van KVV was tussen 2000 en 2003 het overlijdensscenario in 21% van de NWS-patiënten, en heden ten dage dus in 50%. Opvallend was dat deze beslissing in het cohortonderzoek steeds terug te voeren was op een specifieke trigger: dat kon een nieuwe complicatie zijn, maar ook een voedingssysteem dat niet meer werkte. In tegenspraak met het in de literatuur regelmatig genoemde ‘window of opportunity’, dat wil zeggen een soort kritieke periode waarin behandelbeslissingen kunnen worden genomen, voordat een status quo ontstaat waarin eindeloos wordt doorbehandeld, kwam het ook voor dat na decennia alsnog werd besloten KVV te staken.

Het sterfbed na staken van KVV werd doorgaans als ‘rustig’ omschreven, maar het gebeurde ook vor dat de familie, volgens de behandelend arts, leed onder het ‘uitteren’ van de patiënt (citaat arts). In sommige gevallen verstreken meer dan 10 dagen tussen het staken van de KVV en het overlijden. Zeker 3 artsen werden door de familie van hun patiënt verzocht euthanasie aan de patiënt te verlenen – verzoeken die, in overeenstemming met de geldende regelgeving, niet werden ingewilligd.

We betoogden, in navolging van prof.mr. Eugène Sutorius, dat artsen in Nederland volgens de WGBO een medische behandeling uitsluitend mogen starten of continueren als de behandeling voldoet aan de professionele standaard én als de patiënt



er mee instemt. Terwijl in het buitenland vaak juist gezocht wordt naar argumenten om een behandeling te staken, resulteert dit in Nederland in een omgekeerde bewijslast; de dokter moet zich er van vergewissen dat de behandeling in medische zin juist is, en dat zijn patiënt er consent voor geeft. Bij een patiënt in NWS zijn beide zaken zeer onzeker. De KNMG stelde zoals gezegd dat doorbehandelen voor bij kans op herstel niet gerechtvaardigd is. Maar inmiddels zijn er sterke aanwijzingen dat de toen gehanteerde prognostische grenzen te pessimistisch waren. Bovendien heeft Nederland patiënten en hun naasten jarenlang onvoldoende gefaciliteerd in het herstelproces. Er is een misdiagnosepercentage van 41% en gespecialiseerde revalidatie was decennia niet toegankelijk voor patiënten ouder dan 25 jaar. Ook ten aanzien van het reconstrueren van de mening van de patiënt over de betreffende behandeling is problematisch.

Ik liet zien dat zo een vicieuze cirkel ontstaat. Stap 1: er zijn weinig patiënten in NWS, en hun herstelkansen zijn onduidelijk. Stap 2: zorg wordt ad-hoc en op onvoldoende wetenschappelijke gronden georganiseerd, wat leidt tot misdiagnostiek, therapeutisch nihilisme en onvolledige voorlichting van de naasten van de patiënt. Stap 3: het ontbreken van passende zorg en beschikbare expertise leidt tot de neiging de behandeling voortijdig te staken. Dit brengt ons terug naar stap 1: er zijn weinig patiënten in NWS.

We besloten het artikel door te benadrukken dat het een groot goed is dat levensbelangrijke beslissingen bij deze kwetsbare patiënten in de kliniek worden genomen, en niet in de rechtszaal. Deze professionele autonomie echter kan alleen duurzaam bestaan als ook de mogelijkheden tot herstel van de patiënt optimaal kunnen worden geëxploreerd.

Hoofdstuk 6. Laat herstel van bewustzijn

Tijdens het cohortonderzoek werden bij vier patiënten in NWS onverwacht laat tekenen van bewustzijn geobserveerd. We vroegen ons af of deze casus de ideeën over het te pessimistisch zijn van de lang gehanteerde prognostische grenzen zouden ondersteunen. Na uitgebreide bestudering van de dossiers en gesprekken met de



families van de patiënten, concludeerden we dat in alle gevallen het herstel binnen de verwachte termijnen was opgetreden, maar dat het (soms jarenlang) niet was opgemerkt of niet als zodanig werd geïnterpreteerd. Het gevolg was een ernstige diagnostische vertraging.

Hoofdstuk 7. Discussie

In de algemene discussie worden de belangrijkste bevindingen van het proefschrift nog eens op een rij gezet, en kijken we naar de toekomst. Ten tijde van de beoogde afronding van dit promotietraject zijn er talrijke hoopgevende maatschappelijke en wetenschappelijke ontwikkelingen die tot snelle verbetering van de situatie van NWS-patiënten en hun naasten zouden moeten kunnen leiden.

In 2016 is ‘Expertisenetwerk Ernstig Niet-aangeboren hersenletsel na coma’, kortweg ‘EENnacoma’ opgericht met als doel de ketenzorg voor mensen met langdurige bewustzijnsstoornissen (LBS) en andere uitingsvormen van zeer ernstig hersenletsel beter wetenschappelijk onderbouwd en beter passend te maken. Het rapport ‘Naar meer bewustzijn: passende zorg voor mensen met LBS’ dat door leden van EENnacoma in samenwerking met de Hersenstichting in 2018 is gepubliceerd, is in feite een blauwdruk voor precies die zorg en heeft al geresulteerd in het opheffen van de beruchte leeftijdsgrens voor gespecialiseerde Vroege Intensieve Neurorevalidatie. Met centrale diagnostiek is een begin gemaakt; vanuit het Leijpark wordt nu op landelijk niveau bij iedere LBS-patiënt nog in het ziekenhuis het bewustzijnsniveau vastgesteld middels de CRS-R. Dankzij een implementatiesubsidie van de Hersenstichting kan hieruit de komende twee jaar een operationeel outreaching team van experts groeien, gekoppeld aan mogelijkheden voor aanvullende diagnostiek en een landelijke registratie. Bovendien biedt het KPMG-rapport over expertisecentra in de langdurige zorg houvast in het verder professionaliseren van EENnacoma tot een landelijk dekkend, academisch netwerk.

Ten aanzien van onderwijs pleit ik allereerst voor het toevoegen van een disclosure aan



reanimatietrainingen, zodat iedere zorgprofessional en of toegewijde leek voortaan weet dat voor deze invasieve procedure ‘baat het niet, dan schaadt het misschien wel’ geldt. Medisch studenten zouden tijdens hun opleiding in aanraking moeten komen met de verschillende uitkomsten van ernstig niet-aangeboren hersenletsel. Specialisten ouderengeneeskunde zijn, ondanks de naam van het specialisme, goed toegerust om volledige, persoonsgerichte en duurzame zorg aan ook jongere patiënten met complexe neurologische aandoeningen te verlenen, maar verdienen wel de mogelijkheid om een bijzondere bekwaamheid op dit gebied te kunnen behalen. EENnacoma heeft inmiddels al een competentieprofiel opgesteld voor specialisten ouderengeneeskunde en revalidatieartsen die specifiek LBS-patiënten behandelen.

Ten aanzien van onderzoek kan Nederland als de ideale context voor studies naar LBS worden beschouwd, zowel voor epidemiologische studies vanuit de hyperacute fase, als voor kwalitatief onderzoek naar besluitvorming en overlijden.

Het proefschrift besluit met de aansporing vanaf nu steeds in nauwe verbinding, over de kunstmatige barrières tussen specialismen, eerste en tweede lijn, en praktijk en wetenschap heen, samen te werken aan een zo goed mogelijk onderbouwde en op de persoon afgestemde zorg voor mensen met een langdurige bewustzijnsstoornis.





10

RÉSUMÉ



Chapitre 1. Introduction

Le syndrome d'éveil non répondant (ENR), précédemment connu sous le nom « d'état végétatif chronique », est l'une des pires conséquences de survie suite à des lésions cérébrales acquises. Les patients ENR ouvrent les yeux spontanément et respirent d'une manière autonome, mais ils ne montrent que des réactions réflexes. Le fait que des patients dans un tel état puissent rester en vie est un phénomène nouveau et ce phénomène peut être considéré comme le revers de la médaille des progrès médicaux. Dans les 50 dernières années, les chances de survie après un arrêt cardiaque, un traumatisme crânien ou hémorragie cérébrale ont augmenté en créant le scénario des survivants qui ne démontrent aucune preuve de l'existence d'un état de conscience résiduelle.

En sciences médicales, nous avons cherché à connaître l'activité cérébrale des patients hyporesponsifs depuis les années 1990. La population des patients considérés hyporesponsifs était hétérogène : une partie des patients démontrait des preuves de l'existence d'un état de conscience résiduelle, même s'ils n'étaient pas capables de communiquer ou d'utiliser des objets d'une manière fonctionnelle. Cet état est nommé l'état pauci-relationnel (EPR). Les patients dans un tel état peuvent ressentir des douleurs et leurs chances d'amélioration sont plus grandes que celles des patients ENR. Malgré les progrès au niveau de l'imagerie, comme l'imagerie en résonance magnétique fonctionnelle, il n'existe toujours pas de norme de diagnostic pour définir le niveau de l'état de conscience.

Dans la pratique médicale, souvent hors des hôpitaux, les médecins portent une grande responsabilité pour les patients ENR et EPR. Pour ces patients, comme l'écrit en 2012 le spécialiste en médecine gériatrique et philosophe Bert Keizer, on ne peut pas s'attendre à un réveil comme « la Belle au Bois Dormant ». Une grande quantité des publications scientifiques décrit la réalité pour les patients en soins de longue durée aux Pays-Bas. L'intérêt dans ce sujet trouve ses racines en 1990, quand un débat social intense a eu lieu sur des questions de fin de vie d'une jeune femme, Ineke Stinissen, en ENR depuis des



années en raison d'une erreur d'anesthésie pendant une césarienne. La publication d'un cas ressemblant au cas de Madame Stinnissen, dans lequel le spécialiste en médecine gériatrique a décidé d'arrêter toute nutrition et hydratation artificielle (NHA), a mené à la publication des rapports du *Gezondheidsraad* (en 1994) et du *KNMG* (en 1997). Dans ces rapports l'arrêt de NHA est considéré autorisé dans les cas de troubles de conscience sans espoir d'amélioration, et la continuation de NHA est même considérée comme *non autorisée* dans ces cas. De cette manière, la responsabilité des décisions sur la continuation de NHA est dans les mains des médecins traitants et non pas dans les mains des tribunaux.

Malgré les clarifications sur les limites du traitement des patients ENR, la thérapie et les soins pour ce groupe de patients restaient non optimisés pendant les 20 ans qui suivirent. La réhabilitation intensive était disponible seulement pour les patients en dessous de l'âge de 25 ans et elle n'était pas reconnue officiellement comme une réhabilitation spécialisée. Au même moment, les soins de longue durée se développaient vers un secteur très spécialisé et d'une grande qualité, avec des spécialistes comme médecins traitants. Plusieurs institutions spécialisées se sont créées, dans lesquelles les soins adaptés à ce groupe de patients étaient combinés avec de la recherche scientifique, malgré un manque de financement pour ce secteur.

Les connaissances scientifiques sur les caractéristiques de base d'ENR restent limitées, malgré les efforts au niveau des soins et au niveau de la compréhension du substrat neurophysiologique de la conscience. Par exemple, le nombre exact de patients qui se trouve dans cet état dramatique est inconnu, ainsi que la réponse à la question du pronostic à long terme.

Le but de cette thèse est d'agrandir les connaissances dans ce domaine et de donner les réponses à ce genre de questions en relation avec le débat international sur la continuation des thérapies qui mènent à un prolongement de vie des patients ENR. Quelle est la prévalence d'ENR aux Pays-Bas et dans d'autres pays ? Comment se développe l'ENR, quelles sont les étapes de rétablissement, et, en cas de décès, comment



se passe la fin de vie de ces patients ? Comment ces connaissances peuvent-elles se traduire vers des soins plus adaptés pour ce groupe de patients ?

En 2011, j'ai eu l'opportunité de combiner la recherche avec une spécialisation en médecine gériatrique grâce à l'association *Beroepsopleiding Huisartsen*. Cette thèse est donc le résultat d'un échange continu de la science, de l'éducation et de la vie pratique.

Chapitre 2. Une revue systématique de la littérature sur la prévalence d'ENR

Au début de cette recherche nous avons étudié la littérature internationale pour avoir une idée des chiffres de prévalence d'ENR. Nous avons cherché des études transversales sur la prévalence ponctuelle ou la prévalence de période d'ENR dû aux causes aiguës dans la population générale dans les bases de données suivantes : Medline, Embase, the Cochrane Library, CINAHL et PsycINFO. Nous avons aussi incorporé les données « grises » comme les rapports des gouvernements. 14 des 1032 articles répondaient aux critères d'inclusion. Les chiffres de prévalence divergeaient de 0.2 jusqu'à 6.1 patients pour 100.000 personnes ; il y avait 30 fois plus de patients en Lombardie en Italie qu'aux Pays-Bas. Une grande variation était aussi présente au niveau de la qualité des études effectuées. Nous avons donc tiré la conclusion qu'il n'y a pas de chiffres de prévalence solides disponibles dans la littérature internationale.

Chapitre 3. Une étude de prévalence d'ENR

A la suite de cette recherche systématique, nous avons effectué une étude nationale sur la prévalence d'ENR au printemps 2012, avec le but d'identifier tous les patients institutionnalisés et de vérifier leur diagnostic en utilisant l'échelle *Coma Recovery Scale-Revised* (CRS-R). Nous avons reçu une réponse d'une grande partie des hôpitaux, des centres de réhabilitation et des maisons de retraite (96-100%), mais seulement 52 des 270 membres (20%) de l'ordre des médecins spécialisés en handicaps mentaux ont accepté à notre demande d'information. 72 patients répondant aux critères d'ENR ont été identifiés par leurs médecins traitants. Nous avons trouvé des signes de conscience chez 41% de ces patients en utilisant l'échelle CRS-R ; en réalité, ces patients étaient



en EPR ou étaient capables de communiquer ou d'utiliser des objets d'une manière fonctionnelle.

Le diagnostic ENR était confirmé chez 24 patients qui ne démontraient que des réactions réflexes. En revanche, le diagnostic de 9 patients n'a pas été vérifié à cause d'un manque de consentement (7 patients) ou d'une amélioration du niveau de la conscience entre le moment de l'inclusion dans l'étude et ma visite de diagnostic dans leur département (2 patients). La prévalence d'ENR était donc de 24-33 patients institutionnalisés qui se trouvaient en ENR au moins un mois après un incident cérébral aigu, correspondant à 0.1-0.2 patients sur 100.000 personnes de la population générale. Les patients étaient âgés de 27 à 73 ans et étaient en ENR depuis 5 ans en moyenne. Sur les 24 patients, 12 patients se trouvaient en ENR après une réanimation « réussie » et pour 7 patients l'arrêt de la circulation était dû à un incident cardiaque. 83% des patients vivaient dans une maison de retraite. Pour plusieurs patients qui avaient longuement dépassé la période dans laquelle une amélioration du niveau de la conscience pouvait être attendue (jusqu'à 25 ans après l'incident), il n'y avait pas de restrictions aux traitements, ce qui permettait parfois même une nouvelle réanimation.

Chapitre 4. Comparaison avec une recherche antérieure

Après la publication des données du Chapitre 3 dans le journal JAMDA, nous avons comparé les résultats avec la recherche antérieure. Ces résultats ont été publiés dans un article descriptif dans le journal *Tijdschrift voor Geneeskunde*. Nous avons décrit la perspective des patients ENR aux Pays-Bas en comparant nos résultats avec une étude effectuée en 2003, malgré les différences méthodologiques entre ces deux études (en 2003, seulement 9,4% des diagnostics ont été vérifiés et seulement les habitants des maisons de retraite étaient inclus).

Chapitre 5. Une recherche de cohorte d'ENR

Nous avons commencé une étude de cohorte dynamique et observationnelle juste après l'étude de prévalence en 2012, y incluant chaque patient ENR. Sur une période de 6 ans,



nous avons établi le niveau de conscience, les caractéristiques cliniques, les aspects de soins et les scénarios de fin de vie de ces patients. Il y avait des problèmes avec cette étude au niveau épidémiologique : le taux de mortalité élevé et les soins fragmentés empêchaient l'inclusion des patients et j'ai perdu contact avec des patients après un suivi de plusieurs années. Néanmoins, nous avons obtenu les données de 31 patients ENR, nous permettant de tirer des conclusions pertinentes.

Les patients avaient en moyenne 41 ans au moment de la lésion cérébrale. L'encéphalopathie postanoxique causée par un arrêt de circulation était la cause prévalente, en correspondance avec notre étude de prévalence. Un patient seulement avait accès à la réhabilitation spécialisée aux Pays-Bas. Le diagnostic du niveau de conscience manquait ou était erroné dans le compte-rendu de l'hôpital dans 79% des patients.

Sur 31 patients, 18 sont décédés pendant la période d'observation de l'étude : dans 50% des cas la mort suivait la décision du spécialiste en médecine gériatrique d'arrêter la NHA. Entre 2000 et 2003, 21% des patients décédaient après l'arrêt de NHA, soit ça a augmenté jusqu'à 50%. Remarquablement, la décision d'arrêter la NHA suivait un événement déclencheur dans la plupart des cas, par exemple, une nouvelle complication ou un système de nutrition qui ne fonctionnait plus. Pour certains patients, la décision d'arrêter la NHA était prise des décennies après l'incident, contrairement au concept de la « fenêtre de l'opportunité » qui est décrit dans la littérature, qui fait référence à une période critique durant laquelle les décisions sur l'abstention thérapeutique sont prises et après laquelle une situation de statu quo s'installe et le traitement continue sans fin.

En général, la famille décrit le décès du patient après l'arrêt de NHA comme une mort en paix, mais il y avait des situations où la famille ressentait une souffrance à voir le patient « s'émacier » (une citation d'un médecin). Dans certains cas, la période entre l'arrêt de NHA et la mort était de plus de 10 jours. Au moins 3 médecins ont eu une demande d'euthanasie de la part de la famille du patient, des demandes qui ne pouvaient pas être acceptées, conformément à la réglementation en vigueur.



Suite aux idées du Prof.mr. Eugène Sutorius, nous avons argumenté que selon le droit Néerlandais, les médecins aux Pays-Bas peuvent commencer ou continuer un traitement médical seulement si le traitement est en correspondance avec le standard professionnel et si le patient donne son consentement. Cette interprétation mène à une charge de preuve inversée: à l'étranger les médecins cherchent des arguments pour arrêter le traitement, alors qu'aux Pays-Bas le médecin doit s'assurer que le traitement est une bonne décision médicale et que le patient donne son consentement. Dans le cas des patients ENR, ces deux questions ne peuvent pas obtenir des réponses avec certitude. Le *KNMG* a déclaré que la continuation du traitement ne peut pas être maintenue quand on ne peut plus s'attendre à une amélioration du niveau de conscience. Cependant, les chiffres pronostiqués à l'époque de la déclaration du *KNMG* étaient probablement trop pessimistes. En plus, les options de réhabilitation et l'accompagnement des familles aux Pays-Bas étaient insuffisants pendant des années. Il y avait un taux de diagnostic erroné de 41% et pendant plusieurs décennies la réhabilitation spécialisée était accessible seulement aux patients âgés de moins de 25 ans. L'interprétation de l'avis du patient sur les traitements est aussi compliquée.

J'ai démontré qu'on arrive ainsi à un cercle vicieux. Première étape : il existe un nombre limité de patients ENR et leur pronostic n'est pas clarifié. Deuxième étape : les soins sont organisés d'une manière *ad hoc* avec une base scientifique insuffisante, menant aux diagnostics erronés, un nihilisme thérapeutique et une information incomplète aux familles des patients. Troisième étape : le manque de soins adaptés et d'expertise peuvent entraîner une abstention de traitement précoce. Cela nous ramène à la première étape : il existe un nombre limité de patients ENR.

Nous avons conclu l'article en faisant remarquer que dans ce genre de situations, il est préférable que la décision de fin de vie soit prise par le médecin traitant et non par les tribunaux. Cette autonomie professionnelle ne peut perdurer que tant qu'il est possible d'explorer les possibilités de rétablissement du patient.



Chapitre 6. Récupération tardive ou découverte de conscience tardive

Au cours de l'étude de cohorte, chez quatre patients ENR, des signes de conscience ont été tardivement détectés de manière inattendue. Nous nous sommes demandés si ces cas reflètent l'idée que les délais pronostiqués établis pour ENR sont trop pessimistes. Après une analyse approfondie des dossiers médicaux et infirmiers, ainsi qu'une écoute des comptes rendus de la récupération par la famille du patient, nous avons conclu que, dans tous les cas, la récupération s'était bien déroulée dans les délais prévus. Cependant, ces changements importants sont passés inaperçus ou ont été mal interprétés, ce qui a entraîné un retard diagnostique important.

Chapitre 7. Discussion

Dans la discussion générale, je donne un résumé des conclusions de cette thèse et nous envisageons de futurs développements. A l'heure d'écrire les derniers mots de cette thèse, de très prometteurs développements scientifiques et sociaux permettent d'envisager une amélioration rapide dans la situation des patients ENR et de leurs familles.

Le réseau d'expertise pour les patients avec des lésions cérébrales acquises après un coma *EENnacoma* est créé en 2016. Il a pour but d'améliorer les soins pour les patients avec des troubles de conscience ou présentant d'autres symptômes des lésions cérébrales acquises, mais aussi de développer des soins plus adaptés et basés sur des connaissances scientifiques. En 2018, le réseau *EENnacoma* a publié un rapport en collaboration avec l'association des maladies cérébrales (le *Hersenstichting*) : le rapport « Vers plus de conscience : les soins adaptés pour les gens atteints des troubles de conscience » représente un plan directeur pour l'amélioration des soins. Ce rapport a déjà résulté dans l'abolition de la limite d'âge notoire qui existait pour accéder à la réhabilitation spécialisée. Nous avons commencé à centraliser les diagnostics: chaque patient hospitalisé avec des troubles de conscience est diagnostiqué par un employé du centre de réhabilitation *Leijpark* pour vérifier le niveau de conscience en utilisant l'échelle CRS-R. Grâce à une subvention du *Hersenstichting*, ce réseau d'employés spécialisés peut être agrandi dans les années suivantes, en combinaison avec un registre national et



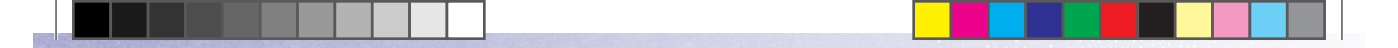
des options de diagnostic supplémentaires. De plus, un rapport du *KPMG* sur les centres d'expertise des soins de longue durée offre un point d'appui pour la professionnalisation de *EENnacoma* vers un réseau académique national.

Je préconise l'ajout d'une divulgation d'informations pendant les cursus de réanimation, pour informer les professionnels de santé et les laïques dédiés que cette procédure invasive peut non seulement être non-efficace, mais même nocive dans certains cas. Les étudiants de médecine devraient être mis en contact avec les survivants des lésions cérébrales atteints de différentes manières. Les spécialistes en médecine gériatrique sont – malgré le nom de la spécialisation – bien adaptés aux soins de longue durée pour les jeunes patients avec des maladies neurologiques complexes, mais ils devraient avoir la possibilité de se spécialiser plus dans ce groupe de patients avec des troubles de conscience. *EENnacoma* a créé un profil de compétences pour les spécialistes en médecine gériatrique et les médecins de réhabilitation qui traitent ce groupe de patients.

En ce qui concerne la recherche scientifique, le contexte des Pays-Bas est idéal pour des études épidémiologiques depuis la phase hyper aigue et pour des études qualitatives sur les décisions de commencement et d'abstention de traitement des patients avec des troubles de conscience.

Je termine cette thèse avec un encouragement : nous devrions créer des soins avec une base scientifique, et adaptés aux patients avec des troubles de conscience, en brisant les barrières artificielles entre les spécialistes concernés, les hôpitaux et les soins primaires, la science et la vie pratique.





11

DATAMANAGEMENT



Dit proefschrift is gebaseerd op de resultaten van onderzoek dat werd uitgevoerd in overeenstemming met de Verklaring van Helsinki (<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-humansubjects/>) en de Gedragscode voor Gezondheidsonderzoek⁽¹⁾. De gegevens die in het kader van de beschreven studies zijn verzameld, zijn gearriveerd volgens de Findable, Accessible, Inoperable and Reusable (FAIR) principes⁽²⁾.

Informed consent

De vertegenwoordigers van alle in het proefschrift beschreven patiënten gaven toestemming voor deelname aan de betreffende onderzoeken. Papieren versies van de informed-consentformulieren worden opgeslagen in het afgesloten archief van de afdeling Eerstelijns geneeskunde van het Radboudumc (M245.-2.053).

Soorten data in dit proefschrift

Systematische review van prevalentiestudies:

- De resultaten van de zoekstrategie zijn opgeslagen in EndNote in de vorm van .enl-bestanden en bevatten ook de onderzochte full-text artikelen.
- Alle data-extracties en tabellen zijn opgeslagen in Word .docx bestanden.

Prevalentiestudie:

- De resultaten van de identificatiefase bevinden zich in Excel-bestanden.
- De data die via elektronische vragenlijsten werden verzameld zijn opgeslagen als .csv-bestanden.
- De observatieschalen worden in papieren versie bewaard in het afgesloten archief van de afdeling Eerstelijns geneeskunde van het Radboudumc (M245.-2.053).
- De complete databestanden zijn zowel als Excel-bestanden (.xls) als als SPSS-bestanden (.sav) opgeslagen.

Cohortstudie:

- Alle kwantitatieve gegevens zijn opgeslagen in een ProMISe-database, conform de GCP-richtlijnen, en bewaard als .sav-bestanden.



Beveiligde dataopslag

Alle elektronische gegevens zijn opgeslagen op de H-schijf van de afdeling Eerstelijnsgeneeskunde van het Radboudumc in map H:\OZ-Ouderen-Langdurige-Zorg\OLZ-AIOTO1-NWS. De data zijn geanonimiseerd en worden bewaard voor een periode van 10 jaar. Alle originele gegevens die op papier zijn vastgelegd, worden opgeslagen in het afgesloten archief van de afdeling eerstelijnsgeneeskunde (M245.-2.053).

De opvolger van dr. J.C.M. Lavrijsen neemt, na afloop van de bewaartermijn, het besluit of de onderzoeksdata vernietigd kunnen worden of voor een langere periode beschikbaar moeten blijven. In het laatste geval wordt de bewaartermijn opnieuw vastgesteld. Het Radboudumc is verantwoordelijk voor dagelijkse back-up van de bestanden op de H-schijf.

Beschikbaarheid data

Alle data zijn, op grond van een redelijk verzoek, op te vragen via dr. J.C.M. Lavrijsen. Het eventueel beschikbaar stellen van data gebeurt in overleg met de promovendus.

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2. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 2016;3:160018. (doi):10.1038/sdata.2016.18.





12

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- 2020** Kondziella D, Naccache L, **Van Erp W**, et al. EAN Guideline on the Diagnosis of Coma and other Disorders of Consciousness. *European Journal of Neurology*. 23(10): 14151. IF: 4.3 - Ranking: Q1
- Arnts H, **Van Erp WS**, Lavrijsen JCM, Van Gaal S, Groenewegen H, Van den Munckhof P. On the pathophysiology and treatment of akinetic mutism. *Neuroscience & Biobehavioral Reviews*. 112:270-278. IF: 8.0 - Ranking: Q1
- van Erp WS**, Lavrijsen JCM, Vos PE, Laureys S, Koopmans RTCM. Unresponsive wakefulness syndrome: Outcomes from a vicious circle. *Annals of Neurology*. 2020 Jan;87(1):12-18. IF: 10.2 - Ranking: Q1
- Arnts H*, **Van Erp WS***, Boon LI, Bosman CA, Admiraal MM, Schrantee AM, Pennartz CMA, Schuurman R, Stam CJ, Van Rootselaar AF, Hillebrand A, Van den Munckhof P (* = equal contribution). Awakening after a sleeping pill: restoring functional brain networks in severe brain injury. *Submitted*
- 2019** **van Erp WS**, Aben AML, Lavrijsen JCM, Vos PE, Laureys S, Koopmans RTCM. Unexpected emergence from the vegetative state: delayed discovery rather than late recovery of consciousness. *Journal of Neurology*. 2019 Dec;266(12):3144-3149. IF: 3.8 - Ranking: Q1
- 2018** Zadoks JM, Gijzen R., **Van Erp WS** et al. Passende zorg voor mensen met langdurige bewustzijnsstoornissen. *De Hersenstichting*, 2018. IF: does not apply - Ranking: does not apply
- 2017** Lavrijsen JCM, **Van Erp WS**. Als bewustzijn niet terugkeert... Wat dan? Syllabus bij voordracht Biemondcursus, 2017. IF: does not apply - Ranking: does not apply
- Vink P, Lucas C, Maaskant JM, **van Erp WS**, Lindeboom R, Vermeulen H. Clinimetric properties of the Nociception Coma Scale (-Revised): A systematic review. *European Journal of Pain*. 2017 Oct;21(9):1463-1474. doi: 10.1002/ejp.1063. IF: 3.0 - Ranking: Q1
- 2016** **van Erp WS**, Lavrijsen JC, Koopmans RT. The unresponsive wakefulness syndrome: Dutch perspectives. *Nederlands Tijdschrift voor Geneeskunde*. 2016;160:D108. IF: does not apply - Ranking: does not apply
- Rietveld A*, **van Erp WS***, Vos PE, Post B, Zandbergen EGJ, Lavrijsen JCM A (* =



equal contribution). Prolonged disorders of consciousness: diagnosis, prognosis and treatment. Tijdschrift voor Neurologie en Neurochirurgie. vol 117 – nr.3 – september 2016 IF: does not apply – Ranking: does not apply

- 2015** **Van Erp WS**, Lavrijsen JCM, Bor H, Vos PE, Laureys S, Koopmans RTCM. Prevalence, characteristics and treatment limitations of institutionalized patients in a vegetative state/unresponsive wakefulness syndrome. JAMDA, 2015;16(1):85 e9– e14. IF: 5.3 – Ranking: Q1

Roets-Merken L; Draskovic I; Zuidema S; **Van Erp WS**; Graff M; Kempen G; Vernooij-Dassen M. Effectiveness of psychosocial interventions in improving emotional and functional status in hearing, visually or dual sensory impaired older adults: A systematic review with meta-analyses. Clinical Rehabilitation, 2015 Feb;29(2):107–19. doi: 10.1177/0269215514542639. Epub 2014 Jul 15. IF: 2.9 – Ranking: Q1

- 2014** **Van Erp WS**, Lavrijsen JCM, van de Laar F, Vos PE, Laureys S, Koopmans RTCM. The prevalence of the vegetative state: a systematic review. European Journal of Neurology, 2014;21(11):1361–8 IF: 4.6 – Ranking: Q1

- 2013** Butler C *, **Van Erp WS** *, Bhaduri A, Hammers A, Heckemann R, Adam Zeman A (*= equal contribution). Magnetic resonance volumetry reveals focal brain atrophy in transient epileptic amnesia. Epilepsy & Behaviour, 2013 Sep;28(3):363–9. IF: 2.6 – Ranking: Q2

- 2012** **Van Erp WS**. Even voorstellen... Specialisten ouderengeneeskunde in opleiding tot onderzoeker. Tijdschrift voor Ouderengeneeskunde (2012/01). IF: does not apply – Ranking: does not apply

- 2011** **Van Erp WS**, Bakker NA, Ariës MJ, Vroomen JP. Opsoclonus and multiple cranial neuropathy as a manifestation of neuroborreliosis. Neurology 2011 Sep 6;77(10):1013–4. IF: 7.6 – Ranking: Q1

Van Erp WS, Tromp SC. De klinische waarde van carotisauscultatie. Tijdschrift voor Neurologie en Neurochirurgie 2011;112:249–51. IF: does not apply – Ranking: does not apply





13

RIHS PHD PORTFOLIO

Name PhD candidate: WS van Erp
Department: Primary Care
Graduate School: Radboud Institute for Health Sciences
PhD period: 01-09-2011 - 01-12-2019
Promotor(s): Prof. dr. RTCM Koopmans, prof.dr. S Laureys (Université de Liège)
Co-promotor(s): Dr JCM Lavrijsen, dr. PE Vos (Slingeland Ziekenhuis)

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
• NCEBP introduction, Radboudumc	2011	0.5
• Course on digital tools, Radboudumc	2012	0.1
• Basic course for clinical investigators (BROK) Radboudumc	2012	1
• NCEBP Academic writing Radboudumc	2012	0.1
• Workshop on scientific integrity by prof.dr. Evert van Leeuwen, Radboudumc	2012	0.1
• Course on Endnote, Radboudumc	2012	0.1
• NCEBP workshop networking (RadboudUMC)	2013	0.1
• Biostatistics course, Julius Center, University of Utrecht	2013	2
• BROK registration renewal, UMC Utrecht	2016	0.5
• Personal leadership course, My-doc	2020	1
b) Seminars & lectures (see also below)		
• Fellowship Seminar Dr Jelle Goeman – Multiple testing for exploratory research (LUMC/ RadboudUMC), 29 May 2013	2013	0.1
c) Symposia & congresses		
• World Congress of the International Brain Injury Association, Edinburgh	2012	
• Verenso Congress: oral presentation & 2 posters	2012	
• 6th International Symposium in Brain Death and Disorders of Consciousness, Havana, Cuba: oral presentation	2013	
• Dutch Society of Neurology, scientific meeting: poster	2014	
• RIHS laptop presentation	2014	
• World Congress of the International Brain Injury Association, San Francisco: poster	2014	
• Hersenletselcongres 2015: oral presentation	2015	
• Symposium on medical leadership, Erasmus MC	2015	
• Verenso Congress: oral presentation	2015	
• World Congress of the International Brain Injury Association, The Hague: invited oral presentation	2016	
• Hersenletselcongres 2018: oral presentation	2018	
• World Congress of the International Brain Injury Association, Toronto: invited oral presentation	2019	
• Hersenletselcongres 2019: oral presentation	2019	
• Verenso Congress: keynote lecture	2019	



Other

• Academic specialization in elderly care medicine (formerly known as 'nursing home medicine')	2011-2018	120
• Presentations during internships in Libra Rehabilitation & Audiology, Leijpark; WZH Nieuw Berkendael; Attent Zorg & Welzijn Regina Pacis; ProPersona Winklerkliniek; AxionContinu (15 in total)	2011-2018	4
• Primary Care RadboudUMC monthly PhD meeting	2011-2014	
• Internship at the Coma Science Group, Universit� de Li�ge	2011	
• Broadcast of a childrens' programme on 'coma' on national television at primetime (Het Klokhuis)	2014	
• Presentation Famelab, Radboud University	2015	
• Various interviews in national newspapers and patient organizations' publications	2014 - onwards	
• Radio documentary on the candidate's publication in Annals of Neurology, aired on 4 consecutive weekdays in morning programme on national public radio + live interview	2019	

TEACHING ACTIVITIES

d) Lecturing

• Studium Generale Eindhoven University	2012	
• Lecture for high school students, Campusdag Radboud University	2012	
• Lecture for junior doctors working in long-term care, Me-doc	2012	
• Lecture for students of medicine, Radboudumc	2012	
• Presentation 'Theories of consciousness' for master students Neuroscience, in collaboration with researchers from Victor Lamme's research group, UvA	2012	
• Lecture for residents in Neurology, Radboudumc	2013	
• Lecture for department of Geriatric Medicine, UMC Utrecht	2013	
• Lecture and workshop for residents in emergency care medicine, Radboudumc	2013	
• Presentation for residents in elderly care medicine, LUMC	2014	
• Presentation for residents in elderly care medicine, GERION Amsterdam	2014	
• Lecture during 25-year anniversary GERION, Amsterdam, 2014	2014	
• Lecture for complete medical staff St Lucas Andreas Ziekenhuis	2014	
• Communicating with elderly patients, workshop for students of medicine, Radboudumc (4x)	2014-2015	
• Lecture for Verenso regional assembly Rotterdam	2014	
• Lecture for residents in Neurology, OOR Nijmegen - Arnhem	2015	
• Clinical teaching for neurology & neurosurgery nurses Radboudumc	2015	
• Lecture on 'ondernemend vakmanschap', My-doc	2016	
• Lecture 'sexiness in elderly care medicine', Verenso	2016	
• Lecture for residents in Neurology and Hospital medicine, VUmc	2016	
• Lecture for the entire staff of the department of Neurology, LUMC	2017	
• Lecture for physiatrists, Hoogstraat revalidatie	2018	



- Science Café Enschede 2018
- Lectures for neurosurgery paramedics and nurses, Isala Clinics 2018
- Workshop CRS-R, nursing home Crabbehof 2018
- Lecture for Verenso regional assembly Utrecht 2018
- Formal accredited training for neurologists, Neurologen Zuid West Nederland) 2019
- Lecture during formal accredited regional reference meeting for physiatrists, Tilburg 2019
- Lecture for ICU-nurses and paramedics, Radboudumc 2019
- Lecture for the entire staff of the Neurosurgery department, Erasmus MC 2019
- Lecture during Leidsche Ouderengeneeskunde Dagen 2019

e) Supervision of internships / other

- Supervising a medical student during scientific internship, Radboudumc (completed) 2015
- Supervising a resident in elderly care medicine during her scientific internship (completed) 2015
- Supervising a medical student during scientific internship, Radboudumc (completed) 2017
- Supervising a medical student during scientific internship, Radboudumc (completed) 2019
- Supervising committee PhD student, Libra Revalidatie & Audiologie 2019 - onwards
- Supervising committee junior researcher, nursing home Crabbehoven 2017 - onwards
- Supervising committee junior researcher, nursing home Crabbehoven 2019 - onwards



14

ACKNOWLEDGEMENTS

De patiënten, hun
families en alle
zorgverleners die
meewerkten aan
dit onderzoek

Jan
Lavrijsen

Raymond
Koopmans

**BEGELEIDINGS-
COMMISSIE**

Steven
Laureys

Pieter
Vos

SBOH

SUBSIDIEGEVERS

My-doc

Candy en
Paul

Emmerik,
Idris en Bess

Pappa,
mamma

FAMILIE

Wouter

Sabine, Ard,
Bojan en Fenna



Arjanne
van Leeuwen

Geertje
van de Ven

ONDERZOEKS- COLLEGA'S

De AIOTO-SO's,

Deliane
van Vliet

Annelies
Daanen

Onderzoeksgroep
Niemand tussen
Wal en Schip

Annette
Plouvier

Camille Chatelle,
Athena Demertzi,
Lizette Heine

OPLEIDERS

Larja
de Letter

Harald
Verhaar

Carin
de Kok

Petra
Ladenberg

Marjon van der Meulen,
Oscar Vogels,
Pieter Hilken,
Herman Schippers,
Jorrit Hoff en
Wilma Pellikaan

Fridus van
der Weijden

Elly
Woudstra

Alien
Bartels

VOSON

Chris
Butler

EN NATUURLIJK

Annemarleen

Bert Keizer

Didi Braat

Strijkorkest
Zoroaster

Laurien

Fietsenmakers

Accolade
Zorg

EENnacom

Libra
Revalidatie
&
Audiologie

De bureu

