

Single case reports on late recovery from chronic disorders of consciousness: A systematic review and ethical appraisal

Katja Kuehlmeier,^a Corinna Klingler,^a Eric Racine,^{b,c,d} Ralf J. Jox^a

^a Institute of Ethics, History and Theory of Medicine, University of Munich, Germany

^b Neuroethics Research Unit, Institut de recherches cliniques de Montréal (IRCM), Montréal, Canada

^c Department of Medicine and Department of Social and Preventive Medicine, Université de Montréal, Canada

^d Departments of Neurology and Neurosurgery, Medicine and Biomedical Ethics Unit, McGill University, Montreal, Canada

Abstract

Late recovery from the vegetative state/unresponsive wakefulness syndrome (VS/UWS) three months after nontraumatic brain injury and one year after traumatic brain injury is considered to be exceedingly rare. The VS/UWS is declared permanent after these time frames. Prognosis of recovery from the VS/UWS is central for decisions about life-sustaining treatment and hence of ethical relevance.

Objectives: We aimed to describe single case reports of late recovery from permanent VS/UWS in scientific journals with a focus on the description of improvements and outcomes.

Methods: We conducted a systematic review of single case descriptions searching PubMed and the Cases Database for synonyms of disorders of consciousness and the term “recovery”.

Results: We screened 1406 records and identified 15 single case reports in 17 scientific journals from 1977 to 2012. Recovery was noticed between four and 33 months after brain injury of non-traumatic etiology, and between 15 months and six years after traumatic brain injury with outcomes ranging from minimally conscious state to almost full recovery (re-entering productive work). The reports were heterogeneous, and some of them lacked important information.

Discussion: Single case reports on late recovery exist and call into question the justification for timeframes in established prognostic guidelines. We suggest a systematic approach to follow-up on single cases (e.g. a prospective case registry) to improve the evidence-base for prognosis. We also propose recommendations for an improved reporting and recommend further reflection on the role of case studies of recovery from disorders of consciousness in the discourse on end-of-life decision making.

Keywords: unresponsive wakefulness syndrome, vegetative state, prognosis, end-of-life decision making, late recovery, ethics

Introduction

Disorders of consciousness refer to conditions occurring after severe brain injury, such as coma, the vegetative state/unresponsive wakefulness syndrome (VS/UWS) and the minimally conscious state (MCS). Coma is a transient state during which the patient does not open his eyes and remains unresponsive to his environment. The VS/UWS refers to patients who open

their eyes intermittently but do not show any signs of responsiveness and arguably no awareness [1, 2]. For patients who show signs of responsiveness such as command-following, visual pursuit of objects or gestural yes/no communication, the diagnostic category of MCS was introduced in 2002. According to the Aspen workgroup guideline, a patient emerges from MCS when he reliably and consistently demonstrates functional interactive communication or functional use of two different objects [3]. Evidence on prognosis and potential for recovery in patients with VS/UWS or MCS is scant and subject to different forms of biases such as the self-fulfilling prophecy [4].

Single case reports have a specific clinical and ethical significance when it comes to late recovery of VS/UWS or MCS, especially with regard to the timeframe within which improvements in the patient's cognition or functional status are observed. In disorders of consciousness, time before recovery has paramount ethical importance given that decisions about life-sustaining treatment are heavily based on prognosis which, in turn, worsens with the duration of the disorder [5]. Professional guidelines have offered recommendations about timeframes after which recovery should be considered highly improbable. One of the most influential reports is the consensus statement of the Multi-Society Task Force (MSTF) on Persistent Vegetative State, issued in 1994, which regarded the VS/UWS to be permanent twelve months after traumatic brain injury and three months after nontraumatic brain injury [6]. After this time, recovery of function was considered exceedingly rare and the functional outcome was thought to almost invariably be severe disability. The MSTF based their recommendation on the finding that only five verified cases of late recovery were published in the scientific literature up until 1994 [7–10]. Further case reports were identified by the Task Force but in their opinion provided insufficient information [11, 12]. The British Royal College of Physicians' guideline from 2003 considered a VS to be permanent also twelve months after a traumatic brain injury, but only six months after nontraumatic events [13]. The guideline of the German Society for Neurology on hypoxic en-

cephalopathy, including experts from Switzerland and Austria, does not give recommendations on time until permanency, but discusses the potential of prognostic indicators measured within the first three days after brain injury (e.g. absent pupillary and corneal reflexes; absent somatosensory evoked potentials) [14]. A European guideline also refers to time frames (six and twelve months) after which the question of treatment limitation (respectively “further active therapy of the patient”) may be raised [15].

Professional guidelines usually combine an evidence-based approach including the systematic review methodology with consensus procedures in order to give recommendations on diagnosis, therapeutic procedures or disease management [16]. There are only a few therapeutic measures that have been evaluated for this patient group in (randomized) controlled trials. A systematic review of these measures includes studies on dopaminergic agents (levodopa, amantadine), zolpidem, median nerve stimulation, deep brain stimulation, extradural cortical stimulation, spinal cord stimulation and intrathecal baclofen [17]. Some treatment approaches improved the responsiveness in certain patients, but overall the studies are inconclusive. A Cochrane review of sensory stimulation programs for individuals in coma or VS/UWS revealed no valid evidence to prove or rule out their effectiveness [18].

To our knowledge, no systematic review of cases of late recovery from disorders of consciousness has been conducted yet. If spontaneous late recoveries occur they are often reported by the treating physicians in case reports, and these may be taken up by the patients’ families and the media, having potentially a profound impact on health care practice [19]. There are several potential benefits to clinicians, family members and ethicists to have an understanding of the single case reports of late recovery observed in clinical practice and published in scientific journals. Such a comprehensive review a) could provide descriptions of exemplary courses and outcomes of recovery; b) could indicate how innovative forms of treatment or medical errors may have an impact on the patients’ recoveries and c) allow insights into the circumstances under which patients were followed up and the reports being published. Furthermore, our results could test the validity of the empirical basis of timeframes for prognostication of recovery which have a profound and immediate impact on end-of-life decision-making and a distal impact on public understanding of patients’ prognoses. To shed light on these crucial aspects, we conducted a systematic review to answer the following specific questions: (1) What are the single case reports on recovery from permanent VS/UWS after the time periods specified by the MSTF? (2) How are the late recoveries explained? (3) What are the outcomes of patients? We discuss the findings with respect to their ethical implications, setting the stage for further normative ethical analysis, which is beyond the scope of

this current paper (see for example [20] for a normative ethical analysis on end-of-life decision-making for patients with disorders of consciousness by RJJ).

Methods

We first devised an informal review protocol that specified the different steps to be undertaken. Following the logic of the PICOS acronym (*patients* (P), *intervention* (I), *comparison* (C), *outcome(s)* (O), and *study design* (S)) we decided on the following inclusion criteria. (P) Patients: We included all single case studies on patients that were either in a coma, the VS or the MCS (not patients with Locked-in Syndrome or severe cognitive impairments, but responsiveness exceeding the MCS). (I) Intervention/Comparison: We decided to not exclude any article based on interventions administered. (O) Outcome: Only studies reporting late recovery from disorders of consciousness were included. We defined *late* recovery as an improvement that takes place three months after a non-traumatic brain injury or twelve months after a traumatic brain injury. *Recovery* was defined differently for patients in coma/VS/UWS or MCS. For patients being comatose or in the VS/UWS, recovery was defined as any sign of responsiveness (see criteria for MCS). For patients in MCS recovery was not only defined as emergence from MCS through regaining the ability to communicate verbally (see criteria for emergence from MCS) but could also include significant improvements in responsiveness within the boundaries of MCS from MCS minus to MCS plus [21]. (S) Study Design: We only included single case reports and excluded case series and intervention studies. Intervention studies were understood as investigations that prospectively planned an intervention, involved a study protocol and planned the measurement of outcome parameters. We only included medical case reports or case reports which gave medical details. We excluded short legal case reports as well as commentaries on case reports.

We searched PubMed and the Cases Database (accessible: <http://www.casesdatabase.com>), using a search strategy that consisted of synonyms of the disorders of consciousness (“vegetative state”, “unresponsiveness wakefulness syndrome”, “prolonged coma”, “apallic syndrome”, “coma vigil”, “minimally conscious state”, “consciousness disorders”) connected by the Boolean operator “or”. This list of terms was then linked by the Boolean operator “and” to the term “recovery”. Descriptors from the thesauri of the databases were added to the search strategy where applicable. Additionally we used filters for species (human) and language (English, German) in PubMed. Last searches were conducted on May 16 (PubMed) and May 28 (Cases Database), 2013. In addition we screened the bibliographies of the papers to identify further relevant papers.

The titles of the papers were screened by the first author to discard those articles that were not concerned with recovery from disorders of consciousness. Abstracts of papers that were not discarded were screened by two independent reviewers. The teams who were screening the abstracts always consisted of one medical student and either the first or the second author to ensure having both research and clinical competency in each team. We then sought access to the articles via the local university and the public library. Where necessary, we also contacted the authors. Full texts of the articles were screened independently by KK and CK. All cases were discussed with RJJ (neurologist and expert on disorders of consciousness) before final inclusion.

We developed a data extraction tabloid. Information considered relevant to our research question was the patient's age and gender, diagnosis prior to recovery, duration until recovery, first signs of recovery, outcome, follow-up, and explanation of recovery. Data was extracted as reported by the author (without further interpretation) by either KK or CK, while the respective other controlled the extracted data. As single case stud-

ies are not dependent on statistical analysis we did not have to assess a risk of a statistical bias of results, but focused on reporting quality. As there are no standard reporting guidelines for events of late recovery (like for adverse drug events) [22] we assessed whether information in the areas identified to be relevant (see above) was reported or not. We analyzed whether the reporting was complete and precise enough to allow the reader to appraise the accuracy of the diagnosis and to get a good impression of the outcome of the recovery. We neither evaluated the credibility of the reports nor did we exclude any reports from our analysis due to lack of relevant information. Missing information was noted during data extraction.

Relying on the review by Dixon-Woods we could not identify any standards for cross-case analysis in systematic reviews that fitted our research question [23]. We extracted information from each single case description by means of content analysis using a tabloid of inductive and deductive categories (within-case analysis) as Miles and Huberman have suggested [23]. Then we discussed similarities and differences between the cases, but due to the heterogeneous case reports we did not conduct any quantitative analysis or statistics. Instead we synthesized the data within a narrative summary (see table 1) and reported identified categories and missing data.

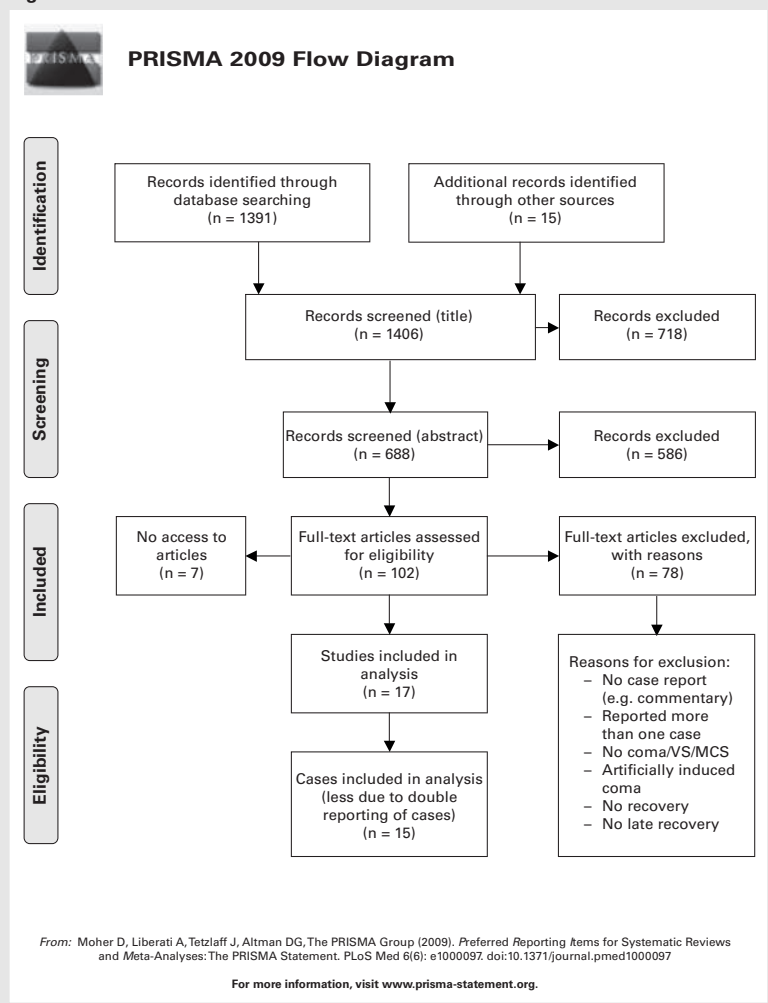
Results

Based on the search strategy, we identified 1406 potentially relevant publications. The application of the screening process yielded a total of 15 cases of late recovery from chronic disorders of consciousness published in 17 scientific journals between 1977 and 2012. We display the search and inclusion process in a PRISMA flow chart (see figure 1).

Description of the publications

The cases were reported in twelve different journals, mostly in the field of medicine, especially neurology and neurologic rehabilitation, except for one report which was published in an ethics journal and written by a philosopher [12]. Some articles were published in journals with high impact factors, such as the *New England Journal of Medicine* or *The Lancet*. The journal that published the most single case reports was *Brain Injury* (n = 5). The purpose of the articles was not always to report late recovery of cognition or improvements in functional status. Sometimes the authors intended to report the validity of prognostic markers (mostly by use of electroencephalography) or to report unexpected recovery despite unfavorable results of the prognostic tests. A few authors intended to report results of experimental treatment attempts outside of clinical studies or re-

Figure 1:



vealed that an improvement followed a change in standard care. The first authors of the reports were working in the following countries at the time of the publication submission: USA (n = 8), Italy (n = 3), Germany (n = 2), UK, Netherlands and Oman (n = 1 respectively).

Course of recovery

We identified ten cases of late recovery after brain injury of nontraumatic causes (see table 1) [8, 12, 24–33] and five cases of late recovery following traumatic brain injury (see table 2) [7, 11, 34–36]. Among the cases were two children [28, 33]. Recovery was noticed between four and 33 months after brain injury of nontraumatic etiology, and between 15 months and six years after traumatic brain injury. In one case the exact point of recovery was not identified, but the patient had improved when the doctors assessed him 12 months after brain injury [28]. Fourteen patients were reported to have been in a VS and one in a prolonged coma. In two articles both diagnoses VS/UWS and MCS had been reported prior to recovery. Eight reports were published before 2002. In one publication, the diagnosis (VS/UWS) and origin of the patient's impairments was unclear because the stroke described seemed not to be responsible for the patients' clinical deterioration [24]. The authors also mentioned a dementia state, but its role remains vague. The reported recovery was either from VS to MCS (mostly in the newer publications), within the spectrum MCS (from MCS minus to MCS plus) or from VS/UWS or MCS to functional communication.

The outcomes were heterogeneously reported with regard to the perspective of the authors and the level of the patient's improvement. Many authors only described improvements in responsiveness (to auditory or visual stimuli); others reported motor improvements in oral feeding, as well as regained cognitive competencies and remaining deficits. Different test instruments were used to measure the outcome: the Glasgow Outcome Scale (GOS), the Glasgow Coma Scale (GCS), the Functional Independence Measure (FIM), the disability rating scale, a participation index or intelligence tests (e.g. the Wechsler Adult Intelligence Scale – R).

The outcomes were found to be related to the follow-up period. The most detailed and accurate description was available for “Kate” who made a remarkable recovery after severe encephalomyelopathy and was followed-up five years after recovery [29–31]. Only one patient was observed to make a recovery that allowed him to re-enter productive work [36]. His cognitive capabilities even allowed him to resume his university studies. He was followed for seven years after a car accident. Other outcomes were rather unfavorable and the patients probably remained dependent on medical and nursing care though the potential for further improvement was rarely discussed.

Explanation

An explanation for the unexpected recovery was missing in six case descriptions. Most authors hypothesized that different therapeutic measures might have advanced the patient's recovery (cranioplasty, drugs such as intrathecal baclofen, an experimental immunological treatment, the use of heated air for ventilation, aggressive efforts by the nursing staff which was not described in detail). Some authors hypothesized that spontaneous changes in the brain might have taken place (axonal regrowth or neurochemical change kick-started by preceding seizures) leading to recovery while others discovered misdiagnosis, although behavioral responses to stimuli had been absent.

Quality appraisal

Given our aims, the most important aspects of the case descriptions were (1) the description of the patient's diagnosis prior to the recovery, (2) the description of the first signs of recovery and (3) the description of the outcome. (1) A good report allowed the appraisal of the diagnosis. Despite mentioning the diagnosis, the guideline followed for diagnosis was not regularly mentioned. An accepted behavioral test instrument (e.g. the CRS-R), which has been available during some of the period covered by the reports, was rarely used to confirm the clinical evaluation. Often the doctor who reported the recovery seemed not to have been involved in the diagnosis. Even though most authors explicitly stated the diagnosis in the title and described them in more detail in the text, it did not always become clear whether the patient was really in the state mentioned or whether the recovery was rather a *discovery* of a misdiagnosed patient. In two cases the authors even acknowledged uncertainty concerning diagnosis (VS or MCS) [26, 29–31]. (2) Reporting of first signs of recovery was generally good. The first signs of recovery were often observed by the author or a team member, identified and described in detail. If they reported a gradual recovery, however, it was sometimes unclear at which point the recovery process started. The time between brain injury and recovery was mentioned precisely (in months) in all but one paper, however, in four cases the way the case was portrayed made it hard to understand exactly when those events had taken place or what event had been identified as first sign of recovery. Even in the articles published after 2002, when guidelines for the diagnosis of MCS were broadly adopted [3], it was not always reflected by the author whether it was an improvement to MCS, within MCS or an emergence from MCS that was identified as a meaningful recovery. (3) The outcome was generally reported in a cursory fashion and rarely described in detail and enriched by validated outcome scales that were appropriate to the patient's condition. The application of un-

specific outcome scales often lead to floor or ceiling effects, which means they were not able to accurately indicate the patient's improvements (either because a large proportion of heterogeneous patients score high or low on the test). The data were hardly comparable across different cases and attempts to standardize the outcome by means of a secondary analysis using the GOS failed due to a lack of description of the functional status in the articles. In addition to that, most authors – especially those who only described short follow-up periods – did not discuss further potentials for improvement which would also have been of interest.

Discussion

We combined the method of systematic review with the content analysis of qualitative single case studies to provide data on late recovery from brain injury. To our knowledge this is the first systematic single case review

on late recovery from disorders of consciousness. While brain damage due to hypoxic brain injury occurs twice as often as traumatic brain injury [15], recovery from hypoxic brain injury is known to be rarer than recovery from traumatic brain injury [5, 6]. However, we found more case reports on late recovery from brain injury of nontraumatic causes. This might be explained by the shorter time after which permanency can be assumed in non-traumatic cases. If we had used the six month cut-off for permanency of nontraumatic brain injuries according to the British and European guidelines, this would have reduced our cases of unexpectedly late recovery from fifteen to six [8, 24, 27, 28, 32, 33], because the other patients would have recovered within the expected timeframe. If recovery occurs within the first six months after the injury, it may be easier detected because the patients may still be in hospital care and not yet discharged home or to long-term care facilities. In addition, because recovery from non-traumatic brain injury is known to be less probable,

Table 1: Cases of late recovery from nontraumatic brain injury

Reference	Age at brain injury (years)	Gender M/F	Cause of the brain injury	Diagnosis prior to recovery (Coma; VS/UWS; MCS; LiS; other)	Interval between brain injury and recovery (months)	First signs of recovery	Outcome*	Last follow-up since recovery (months)
Fellerhoff 2012	73 at stroke; 82 at change	F	Stroke, maybe viral or bacterial infection or dementia	VS/UWS but uttering "Maria"; "deep sleeplike state"; "dementia state"	7	Opened eyes on demand; moved them in the requested direction; eyes followed person; turn head	Responsiveness: looked at the children but no proof that she recognized them, oral: swallow independently; motor: e.g. grab for the bar of the bed or the hands of the grandchildren; later: death as final outcome	8
Pistoia 2008	52	M	Cardiac arrest, CPR	VS/UWS	4	Sustained visual pursuit, reproducible visual fixation, voluntary acts: e.g. followed visual or auditory stimuli, commands	Responsiveness: minimally conscious; test: CRS-R score of 13/23, motor: tetraplegia might have hindered performance of object manipulation (key indicator of emergence from MCS)	no
Al-Adawi 2006	52	M	Subarachnoid hemorrhage (aneurysm); cardiac arrest: anoxic brain injury possible	VS/UWS and MCS	6	Increased awareness of surroundings, verbalizes more and better oriented in time and place	Overall: significant improvements; widespread improvement in his cognitive and functional abilities; tests: PPI improved from 0% to 50–60%, FIM improved from 10% to 60–70%	2
Ford 2006	53	F	Respiratory failure and cardiac arrest	VS/UWS after being responsive	33	Respond to questions with a simple yes/no	Communication: reply to questions with "I don't wanna"; "I no power"; verbalization sporadic, and interrupted by months of silence	no
Goodwin 1993	6	M	Strangulation; cardio pulmonary resuscitation	VS/UWS	Unclear; re-assessment after 12	Clearly related to environment, responded appropriately to voice and receptive language	Vigilance: Patient alert and interactive, test: GCS=15; oral: feed himself, motor: walk with walker; continued improvement in muscle function, communication: receptive language normal, expressive language limited by muscle spasticity; most of language could be understood	Unclear; (2 years after the accident)

Macniven 2003; Wilson 2001; Menon 1998	26	F	Severe encephalomyelopathy	VS/UWS, later MCS	6	Respond to environment; initial signs that level of consciousness was improving, for example articulation of single words and phrases	Motor: severe physical disabilities that require a wheelchair cognitive: intellectual, executive and memory skills largely within the normal range; difficulty in face and emotion expression recognition; almost complete cognitive recovery. communication: severe dysarthria, use of a communication board	60
Rosenberg 1977	43	M	Cerebral anoxia due to cardiac arrest	VS/UWS	17	Alert patient followed two-step commands by blinking, attempting to talk, moving his right hand; full voluntary eye movements and good movements of his tongue, but bilateral facial weakness	Oral: oral praxis normal; visual: a right homonymous hemianopia, motor: severely physically disabled; moved fingers and some control of legs; name parts of the body that were touched, and proprioception intact, cognitive: intellectual functions partly recovered; oriented (person, place, year and time), memory performance impaired, amnesia for time before and after admission; able to name simple objects but could not recognize complex collections; recognize some letters, test: score 100 on verbal section of the WAIS with particular deficits noted on tasks requiring concentration, recent memory skills and learning new information. communication: tell stories and jokes	24
Sara 2007	44	M	Spontaneous subarachnoid hemorrhage due to a ruptured aneurysm	VS/UWS	19 a) or 21 b)	a) Appearance of spontaneous unintentional movements in the second and third finger of the right hand; never reached the level of an intentional movement b) patient started to show aroused emotional responses to external stimuli, mild voluntary activity and partial recovery in cognition, spontaneous vocalization	Oral: eating ice-cream, motor: gradually regained motor abilities with both hands; starting to manipulate objects; unwrapping parcels, peeling tangerines, turning on and off a portable radio receiver, trying to move his wheelchair, communication: able to articulate the name of his son, to give yes/no answers to very simple questions	Unclear; 2 or 4 months
Steinbock 1989	85	F	Stroke	VS/UWS	4.5	Took small amounts of food by mouth and engaged in conversation	Oral: dependent on feeding tube, communication: able to communicate, but often inconsistent in her responses	no
Tsao 1991	5	M	Near-drowning	VS/UWS	7.5	Gradually became aware of parents	Cognition: test: SB: at lower limit of the mildly mentally retarded range; social: good socialization skills; interacted well with friends in games and plays; communication: more recently producing 3–4 word phrases spontaneously; overall: mildly retarded	9

Most recently published articles are described first; *categories derived from inductive content analysis; Abbreviations: M = Male; F= Female; CPR =Cardio-pulmonary resuscitation, Test scales: FIM=Functional Independence Measure, CRS-R=Coma Recovery Scale – Revised; PPI=Patient Participation Index; GCS=Glasgow Coma Score; WAIS= Wechsler Adult Intelligence Scale; SB= Stanford-Binet-Intelligence Scale:

Table 2: Cases of late recovery from traumatic brain injury

Reference	Age at brain injury (years)	Gender: M/F	Cause of the brain Injury	Diagnosis prior to recovery (Coma; VS/UWS; MCS; LiS; other)	Interval between brain injury and recovery (months)	First signs of recovery	Outcome*	Last follow-up since recovery (months)
Sancisi 2009	22	M	Car accident	VS/UWS	19	Consistent behavioral responses; visual pursuit, appropriate smiling, obeying simple commands with left arm	ADL: lives in the community, speaks, walks, undertakes activities of daily living and outdoor leisure activity independently; resumes university studies and has a competitive part-time job test: GOS=Moderate disability	Approx. 84
Faran 2005	28	M	Car accident	VS/UWS	6 a) or 20 b)	a) ERPs in EEG or b) articulating words	Responsiveness: completely aware of his situation, recognized his family and friends, cognitive: anterograde amnesia ADL test: DRS=17	8
Childs 1996	18	F	Motor vehicle accident	VS/UWS	15 a) or 17 b)	a) possible leg flexion and eye closure on two occasions in response to commands b) responses were progressively more consistent	Oral: oral feeding, cognitive: attention span limited, consistent orientation to person only, communication: follow conversations; communicating by words and short phrases; emotive: enjoyed pampering, and her mood was usually euphoric; ADL: remained wheelchair-bound, disabled and dependent for care	43
Arts 1985	18	F	Car accident	VS/UWS	30	Able to nod and lift her leg	Cognitive: regained mental capacity with the exception of a severely defective short-term memory; read and watch television, communication: able to comprehend, communicate; write by means of a typewriter, social: establish relations with well-known persons. ADL: completely ADL-dependent; Further improvements: expected	42
Tanhco 1982	25	F	Motorcycle accident	Coma	72	Opened eyes, responded to objects and conversation. She was able to nod and shake her head accurately in response to questions	Vigilance: alert, oral: feed herself cognitive: decreased retention, memory, integration, communication: speech; ADL: groom herself, moderate assistance for dressing and transfers needed, greater level of independence in activities and vocational productivity was precluded by the severities of her injuries; lives with family	14

Most recently published articles are described first; *categories derived from inductive content analysis; Abbreviations: ADL: Activities of daily living; DRS=Disability rating scale (score); GOS=Glasgow-Outcome Scale

physicians could be more surprised when it occurs, and thus be more inclined to publish these cases. This emphasizes the ethical relevant consequences of guidelines' definitions of timeframes for declaring a condition permanent: if it is set too narrow, some patients may die from withdrawal of treatment who could have otherwise recovered significant functions. Due to our inclusion criteria to only report single case studies we had to exclude reports on a famous case of late recovery [37–40], because this case was published jointly with the description of another patient suffering from TBI (like in other reports e.g. [41–44]). This famous case describes the recovery of a patient from MCS 19 years after brain injury. Upfront, this points out a crucial limitation of our study. We focused on rich reports

of single cases to be able to learn about the reporting of spontaneous recovery and to get detailed information on the courses and outcomes of the recoveries, so we ruled out case series and cohort studies that also contain valid cases of late recovery (e.g. [9, 45–48]). In one of the most recent prospective studies, late recovery of responsiveness was identified in ten patients with long-lasting VS/UWS and six of them further progressed to consciousness [45]. First results of a new and ongoing prospective study using data of a joint patient registry of five German rehabilitation centers aspires to contribute further data on the prognosis of disorders of consciousness [49]. Prospective cohort studies would have been favorable if we were interested in frequencies of late improvements, but they have been crit-

icized for being biased by missing cases that were not registered because early decisions on treatment limitations have been made. Yet, not including articles that reported more than one case can only be justified by a practical reason: we had to decide how many cases were acceptable per report (two or ten?). This line had to be drawn arbitrarily so we decided to only include single case studies.

A further limitation is that we conducted our search in a limited number of databases with a limited variety of keywords and language restriction to German and English and there were papers that we could not access (n=7). Although we screened the relevant papers in pairs of two we consulted the neurologist only in the last step of the inclusion process and cases might have been missed.

Another important case was excluded from our analysis because the first signs of recovery were observed within the first year after traumatic brain injury, yet these signs of progression to MCS at first were not interpreted as signs of recovery by the treating physicians [50–53]. This case is important for the discourse on end-of-life decision making because there was a legal proceeding asking the court for permission to terminate the feeding by gastrostomy tube. It was reported that the patient had previously expressed verbally that she would not wish to continue living in the case of severe brain injury [50]. As a result of a thorough neuropsychological assessment by two independent evaluators the patient was found to be responsive, “sentient and wanted to live”. Remarkably, the patient was followed-up several times up to ten years after brain injury, where she was living in the community with 24-hour care, was capable of communication, oral feeding, and using a wheelchair. Although this case is not a proof of the potential for late recovery in other cases, it demonstrates how important a thorough analysis of the individual’s chances for recovery is.

Appraisal of the clinical evidence

The evidence compiled in our study could be used either to justify continuing life-sustaining treatment beyond a certain timeframe by stating that these cases occur or to justify limiting life-sustaining treatment by pointing out how rarely they are reported in scientific journals and how unfavorable their outcomes are. We propose a third option of encouraging physicians to make detailed single case descriptions available which allow: a) the identification of hypotheses for prognostic markers and indicators for late recovery; b) the identification of treatment errors that could have prevented the patient from recovering earlier; and c) to get insight into the long-term courses of VS/UWS and more importantly of MCS, where there is a lack of long-term data because the diagnostic category has only been in use for a bit more than the last decade. Physicians might be

prone to overestimate the probability of late recovery when consulting case reports like these. When overestimating the probability for late recovery in a case where further improvements will not occur, one could do harm to patients and their families by deciding to prolong the patient’s life without the patient having the potential to ever reaching a level of meaningful recovery. There is also a risk that an overestimated potential for recovery could lead physicians to paternalistically overrule the patient’s autonomous wishes written in an advance directive or expressed orally. As an interview study with next of kin of patients with disorders of consciousness in the long-term care setting indicated, a perceived potential for further recovery might be weighed stronger by the patients’ family caregivers than the patients’ will [54]. A futile prolongation of life would lead to costs without benefits for families and society.

International guidelines, publication bias and bias of perspective

The timeframes in the guidelines developed by the MSTF have been based on only five identified and verified cases of late recovery which served as evidence to propose that prognosis is poor after three or respectively twelve months. This evidence should not be considered sufficient to determine the probability of recovery and was in fact acknowledged to be suboptimal by members of the Task Force themselves. Due to a publication bias, the amount of published case studies cannot answer squarely the question when a VS/UWS should be considered permanent. There are barriers to publishing case reports in peer-reviewed scientific journals like the researchers’ motivation and the peer-review process. A researcher needs to observe the recovery, which probably requires a physician in a double role as researcher and doctor. The clinician has to decide to report, which requires him to be interested in the topic, aware of the value this information could have for colleagues, having the resources and the access to all the relevant information on the patient. In addition, the journal has to accept his report, which could be hindered by objections against the evidence level of single case reports. Those problems are mirrored in the case reports we identified: the quality of the publications was heterogeneous and some reports were lacking information, due to either lack of access to important data or selective reporting. Furthermore, we speculate that researchers in countries where legal cases of treatment withdrawal were recently discussed (e.g. USA, Italy, and Germany) could be more motivated to publish cases of late recovery than researchers in other countries.

Prognostic guidelines recommending timeframes for permanency can lead to self-fulfilling prophecies, meaning that late recoveries are not observed because physicians have decided to stop treatment without

knowing how the patient's condition would have proceeded [5, 19]. The low expectation of recovery might lead to a so called "neglect syndrome" and "therapeutic nihilism" meaning that patients with a poor prognosis are treated with less effort and thus their conditions worsen [55]. This is ethically relevant because it might bias decisions about life-sustaining treatment towards termination and impede research on long-term outcomes of these patients. A clinical culture dominated by "therapeutic nihilism" – where guidelines about timeframes for permanency were being accepted by the treating physician given the lack of evidence-based therapeutic measures – could have further hindered the publication of cases of late recovery.

Although our research cannot determine the statistical probabilities for late recovery, it demonstrates that the established guidelines should be reexamined as late recoveries are (in spite of the described obstacles) still observed and reported. It could be understood from our study that a timeframe of three months is too short to declare a VS/UWS of non-traumatic cause permanent because we discovered ten single-case descriptions of late recovery after this timeframe. Our results at least provide evidence that questions the assumption that these cases occur extremely rarely. That is not to say that our study is able to give information on the chances for late recovery three months after nontraumatic brain injury, which only prospective studies are able to. Furthermore, we assume that a lot of patients remain in the VS/UWS and die from complications but are never published extensively in journals.

Appraisal of ethical implications of the clinical evidence

To provide ethical guidance on decisions about life-sustaining treatment for patients with disorders of consciousness we apply the principles of biomedical ethics [56]. These principles – respect for autonomy, beneficence, non-maleficence, and justice – need to be specified to be applicable for a concrete situation and have to be weighed and balanced against each other.

In the context of life-sustaining treatment for disorders of consciousness, the principle of respect for autonomy may be decisive when the patient prospectively expressed a self-determined and well-reflected will (e.g. by advance directive or orally expressed wishes) against life support in a permanent VS/UWS. The principles of beneficence and non-maleficence demand that the potential benefit that the patient will reap from further treatment does outweigh the harms of the treatment. Potential harms could be the side effects of the treatment or suffering caused by the sequelae of the brain injury (e.g. pain caused by spasticity). The principle of nonmaleficence could especially guide a decision when further treatment is judged to be futile [57]. It has been argued in legal cases that life in a perma-

nent VS/UWS does not benefit the patients because they are permanently unaware and hence a prolongation of life in a chronic VS/UWS is not in the best interest of the patient [58]. The German chamber of physicians does not accept a chronic disorder of consciousness alone as a prerequisite for the limitation of treatment, and refers to the "medical indication" – the treatment proposal of the treating physician when considering the patients best interest [59]. Accordingly they assume that even patients in chronic VS/UWS can still benefit from further treatment because there might be – at least in some cases – potential for improvement. In Great Britain the legal case of "M" stimulated a discussion on the value of life in a MCS, when a judge declined the patient's family's request for withdrawal of treatment – which in their perspective reflected the patient's prospective will – with the reason that M responded positively to some stimuli, in which she could be further supported, and "the importance of preserving life" as being the decisive factor [60, 61]. It could furthermore be argued that the principle of justice would demand that patients and their families should have fair chances to get treatment which might not be the case when the resources for long-term care facilities are rare [20]. In the case of conflicting principles they need to be weighed against each other. In the legal case of M the principle of beneficence was weighed higher by the judge than the principle of respect for autonomy but it was argued that the court's reasoning was flawed and that continued artificial nutrition and hydration was not in this patient's best interests and thus should have been withdrawn [60].

How do our results relate to the discourse on end-of-life decision making? In disorders of consciousness, patient autonomy could only be represented through prospective autonomy or substitutive autonomy because whenever the patient will be able to communicate, he will have improved beyond a MCS. Prospective and substitutive autonomy rely on the availability of valid information to the patient himself or his surrogate decision maker who is most often a non-clinician without expert knowledge on disorders of consciousness.

The physicians' judgment of the patient's best interest as a potential informant for patients or their relatives and important actor in the decision-making process can only be assessed based on the background of valid information about the chances of recovery for analogous patients which requires the availability of valid clinical evidence. The provision of prognostic information has high ethical relevance in these cases. For example, if a citizen – a potential patient – wants to express his treatment wishes for a future state VS/UWS, he needs to balance the potential benefits of a future treatment against the potential harms without knowledge of his own future condition. It could be assumed that most patients would not want to reject treatment measures in acute coma (because chance for recovery and good outcome are reasonably high), but would

want to reject treatment when recovery becomes highly unlikely. Accordingly, advance directive forms often provide the option rejecting treatment in a “permanent” or “irreversible” VS/UWS. But this begs the question when and how chronicity can be established.

Our results show that the existing guidelines which use time frames (e.g. three months after nontraumatic brain injury) to determine permanency are biased because they initially justified their timeframes with biased evidence (scientifically published reports of cases of late recovery available at that time).

Clearly, from an ethical and clinical standpoint, we need better evidence to more accurately declare the time point and clinical condition where the prognosis of a patient with a disorder of consciousness is not uncertain anymore but definitely hopeless. Citizens can then use this information to better express their prospective wishes thereby allowing physicians to respect their appraisal of different outcomes of brain injury like VS/UWS, MCS and others such as recovery above MCS. Our long-term goal should be to improve the evidence for a valid prognostication of recovery from brain injury. Our short term suggestion, until the evidence base will have improved, is to thoroughly inform the general public and families about the different diagnostic groups in disorders of consciousness, the potentials for improvements for the respective patient groups, the probable outcomes and the uncertainty under which they might have to make decisions about the refusal of treatment [19]. They might have to think about timeframes themselves and assess the impact of the duration of a disorder of consciousness as one important variable. This would give patients the chance to balance for themselves for how long they would prefer the potential of improvement against the potential harm of living in a condition where not being able to communicate and potentially suffering from pain which is a clinical aspect of high ethical relevance [62].

(1) An international prospective registry for patients with disorders of consciousness after severe brain injuries

In order to ground end-of-life decisions on a reliable prognosis for the patient, more information is needed on the possibility of late recovery and on the outcomes of those late recoveries. The best way to retrieve this information would be to perform prospective observational studies. This, however, is methodologically difficult in such a heterogeneous and relatively rare spectrum of disorders [63]. An alternative option is an international prospective registry for patients with disorders of consciousness after severe brain injury: it could a) lower the barriers for reporting a case of unexpected recovery, creating an opportunity to also report cases with unfavorable outcomes and b) pool data to improve the information base for decisions about treatment limitation. It could be argued that such a registry may already alter the practice of decision making

for these patients. Psychologically, it could lead to more conservative decision making (waiting longer) because doctors could be afraid of being held responsible legally when the case registry monitors decision-making for the registered cases.

Yet, a registry would allow us to collect better data on the “natural” course of recovery. A computer-based case registry is not a new idea. “The National Traumatic coma data bank” was initially founded by university hospital centers in the US in 1979 for the registration of patient data followed-up after traumatic brain injury [64, 65] and is meanwhile the largest aggregation of trauma registry data ever assembled (see [66]). This data bank only allows the inclusion of cases after traumatic brain injury and is to our knowledge limited to US-American facilities. We recommend an international registry that also includes patients who experienced nontraumatic brain injuries and we recommend a focus on disorders of consciousness.

Naturally there are organizational barriers, like a lack of funding, and research ethics issues to consider (e.g., balancing the storage of private data and the lack of informed consent from the single patient against the high benefit of generating knowledge on affected patients). Further discussion is needed to determine who should have access to the data, e.g. professionals only or providing a platform to inform the general public on overall outcomes and recovery. Such a registry could improve the standards of patient follow-up and therefore improve the evidence base for end-of-life decision making and public discourse.

(2) Quality of case reporting of brain injuries

Given this ethical significance of prognostic information, developing a standard for reporting cases with disorders of consciousness after severe brain injuries would be advisable. Otherwise, the quality of the evidence base could be too limited to usefully inform clinical and ethical discussions. From the appraisal of the quality of the reports we derived initial recommendations for the reporting of single cases of brain injury (see figure 2) that would need to be discussed further with experts from different fields such as neurorehabilitation.

Conclusion

Single case reports of late recovery from disorders of consciousness are published rarely, but they are not a sufficient source of evidence to conclude that after certain timeframes recovery of consciousness can be ruled out. More information needs to be gathered about the course of recovery of patients with disorders of consciousness as a ground for end-of-life decision making. Having reliable information on the probability of recovery is key to the formulation of an autonomous will for or against future treatment and to the judgment of the

Figure 2: Reporting recommendations

As single case reports are an important source of information, initial recommendations for reporting those cases were derived from our results and their analysis.

- Information on patient
 - Date of injury
 - Age at injury
 - Gender
 - Comorbidity
- Type of injury
 - TBI/NTBI
 - Pathological anatomy
- Condition of patient
 - Outcome of Glasgow Coma Scale
 - Eye opening
 - Outcome of behavioral tests
 - Outcome of neuroimaging techniques
 - Outcome of neurophysiologic examinations
 - Outcome of laboratory tests
 - Frequency of examinations
- Treatment administered
- Description of recovery (if it applies)
 - Date of recovery
 - Timeframe until recovery
 - Firsts signs of recovery
 - Course of recovery
 - Final health state/residual deficits
 - Follow-up period
 - Explanation: Hypothesis regarding causal mechanism for improvement
 - Potential for further recovery

patients' best interest. Given the low prevalence of disorders of consciousness like the VS/UWS and MCS, single case studies can play a role in informing those decisions not only as preliminary information that could be pooled and statistically analyzed, but also to inform stakeholders on the courses and outcomes of disorders of consciousness.

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Zusammenfassung

Einzelfallberichte über späte Erholung von Bewusstseinsstörungen. Systematisches Review und ethische Bewertung

Eine späte Erholung von einem Vegetativen Status bzw. einem Syndrom reaktionsloser Wachheit (VS/SRW) wird drei Monate nach einer nicht-traumatischen Hirnschädigung und ein Jahr nach einer traumatischen Hirnschädigung als extrem selten eingeschätzt. Der

VS/SRW wird nach diesen Zeiträumen für chronisch bzw. permanent erklärt. Die Rehabilitationsprognose ist beim VS/SRW zentral für Entscheidungen über lebenserhaltende Maßnahmen und daher von ethischer Relevanz.

Ziel: Unser Ziel war es, Einzelfallberichte von später Erholung aus dem permanenten VS/SRW in wissenschaftlichen Zeitschriften zu sammeln und dabei den Schwerpunkt auf die Beschreibung der Rehabilitationsergebnisse zu legen.

Methoden: Wir führten ein systematisches Review von Einzelfallbeschreibungen durch und suchten in PubMed und einer Fall-Datenbank nach Synonymen von Bewusstseinsstörungen («chronic disorders of consciousness») und dem Begriff Erholung («recovery»).

Ergebnisse: Wir prüften 1406 Einträge und identifizierten 15 Einzelfallbeschreibungen in 17 wissenschaftlichen Zeitschriften zwischen 1977 und 2012. Erholungen wurden vier bis 33 Monate nach nicht-traumatischer Hirnschädigung und 15 Monate bis sechs Jahre nach traumatischer Hirnschädigung beschrieben. Die Ergebnisse («outcomes») reichten vom minimal bewussten Zustand (MCS) bis zur beinahe vollständigen Rehabilitation (Wiedereintritt in die produktive Arbeit). Die Berichte waren heterogen und einigen fehlten wichtige Informationen.

Diskussion: Einzelfallberichte über späte Erholung existieren und stellen etablierte prognostische Leitlinien in Frage. Wir empfehlen ein systematisches Vorgehen, um Einzelfälle zu verfolgen (z.B. ein prospektives Fallregister), um die Evidenz für prognostische Aussagen zu erhöhen. Wir formulieren Empfehlungen für eine verbesserte Berichterstattung von Einzelfällen. Die Rolle von Fallberichten später Erholung für den Diskurs über Therapieentscheidungen am Lebensende sollte Gegenstand weiterer Reflexionen sein.

Resumé

Histoires de cas individuels souffrant de pathologies chroniques de la conscience et qui se sont rétablis: une revue systématique et une évaluation éthique.

Les rétablissements tardifs d'états végétatifs chroniques ou de syndrome d'éveil non répondant (VS/UWS) plus de trois mois après un accident cérébral non traumatique ou plus d'une année après une lésion cérébrale traumatique sont considérés comme excessivement rares. L'état d'un patient VS/UWS est déclaré permanent après ce laps de temps. Le pronostic de rétablissement d'un état VS/UWS est central pour les décisions concernant les traitements de maintien en vie.

Objectifs: Nous avons visé à décrire les cas individuels de rétablissement tardif d'états VS/UWS permanents rapportés dans les revues scientifiques, avec une atten-

tion particulière portée à la description des améliorations et des résultats.

Méthodes: Nous avons conduit une revue systématique des descriptions de cas individuels. Nous avons mené notre recherche sur les sites de PubMed et de Cases Database pour les synonymes de pathologies de la conscience et pour l'expression « rétablissement ».

Résultats: Nous avons examiné 1406 rapports et identifié 15 cas dans 17 revues scientifiques de 1977 à 2012. Le rétablissement a été observé dans la période allant de 4 à 33 mois après un accident cérébral non traumatique, et dans la période allant de 15 mois à 6 ans après une lésion cérébrale traumatique, avec des résultats allant d'un état minimalement conscient (MCS) à un rétablissement presque complet (retour sur le marché du travail). Les compte rendus étaient hétérogènes et il manquait des informations importantes dans certains d'entre eux.

Conclusions: Des histoires de rétablissement tardif existent et mettent en question les directives acceptées concernant les pronostics. Nous suggérons un suivi plus systématique des cas individuels (p. ex. un registre international) pour améliorer le pronostic. Nous proposons aussi des recommandations pour une amélioration dans l'annonce de ces cas et pensons qu'il faut pousser la réflexion sur le rôle des cas de rétablissement tardif dans l'optique des prises de décision concernant la fin de vie.

Correspondence

Katja Kuehlmeier
Ludwig-Maximilians-Universität München
Institut für Ethik, Geschichte und Theorie der Medizin
Lessingstr. 2
D-80336 München

E-Mail: katja.kuehlmeier[at]med.lmu.de

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