Chapter 13
The Ethics in the Management of Patients with Disorders of Consciousness

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Abstract The ethical issues accrued from the study and management of patients with disorders of consciousness are variant and multifaceted. The medical, public and legal controversies are partly shaped by how different people think about pain perception and end of life. Uniform ethical frameworks need to be shaped in order to guide clinicians and caregivers in terms of clinical outcome, prognosis and medical management.

Introduction

The introduction of the mechanical ventilator in the 1950s and the development of intensive care in the 1960s permitted many patients, who would otherwise might have died from apnea, to sustain their vegetative functions and survive their injuries. Paradoxically, in many cases these survivors were nevertheless found to suffer from altered states of consciousness which had never been encountered before [1]. The imminent ethical impact of these profound states of unconsciousness was reflected in the composition of the first bioethical committees discussing the redefinition of life and the concept of therapeutic obstinacy. In 1968 the Ad Hoc Committee of Harvard Medical School published a milestone paper for the redefinition of death as irreversible coma and brain failure [2]. The fact the committee comprised of ten physicians, a theologian, a lawyer and a historian of science, betokened the medical, legal and societal debates that were to follow.

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Consciousness Can Be Defined Clinically

Confusions and controversies are often a matter of definition. One multifaceted term with divergent connotations is consciousness [3]. For example, in a survey among healthcare professionals and students, it was found that although the majority of participants denied the distinction between consciousness and the brain, more than one-third still regarded mind and brain as separate entities [4]. The way we define consciousness is crucial especially in the clinical setting because it may govern our opinions and eventually our actions. From a clinical viewpoint, consciousness is defined as having two components, wakefulness and awareness [5]. Under this definition, many variant altered states of consciousness may be hosted. The most familiar to us all is the transition from conscious wakefulness to deep sleep: the drowsier we become, the less aware we get of our surroundings and of ourselves. This implies that patients in coma and under anaesthesia are unaware because they cannot be awakened, even after painful stimulation. An exception to the way that these two components are related comes from patients in the so-called vegetative state (VS) or, as most recently defined, in unresponsive wakefulness syndrome (UWS) [6, 7]. Patients in VS/UWS typically open their eyes but never exhibit non-reflex voluntary movements indicating preserved awareness. In 2002, the term minimally conscious state (MCS) was introduced to describe those patients who showed more complex behaviours declarative of awareness, such as visual pursuit, orientation to pain or nonsystematic command following. Importantly, patients in MCS remain unable to communicate their thoughts and feelings [8]. Because these signs of consciousness often are small and fluctuating in time, this condition may be challenging to diagnose and to differentiate from the VS/UWS [9]. This is one of the reasons that assisting technologies, by providing data-driven objective evaluations of consciousness level, are becoming all the more an important source of information that clinicians are often refer to in order to increase their clinical verdict, e.g. [10–13]. It has been suggested that once conscious awareness has been identified and its quality is estimated in a noncommunicating patient, this may well be a good reason to preserve life-sustaining aids [14]. However, the moral significance of preserved consciousness has been questioned on the grounds that it may not always be in patients' best interest to continue a severely handicapped life [15]. Below we will see what kind of ethical concerns may arise during the medical management of DOC patients and how healthcare workers and next of kin consider these issues.

Emerging Ethical Issues About Pain

The day-to-day needs of patients with DOC are exclusively covered by the healthcare providers and patients' families and next of kin. Patients with DOC cannot communicate their feelings or experience, but it is not unusual that during cares, they will exhibit facial expressions and/or vocalize. Such behaviours can be

confusing for the carers as they might consider them as reactions to pain. As defined by the Multi-Society Task Force on PVS, "pain and suffering refer to the unpleasant experiences that occur in response to stimulation of peripheral nociceptive receptors and their peripheral and central afferent pathways or that they may emanate endogenously from the depths of human self-perception" [16]. Thus, pain constitutes a conscious experience with a physical (nociception) and a psychological counterpart (suffering). This also suggests that nociception by itself is not sufficient to cause suffering. Such differentiation is reflected on how clinicians perceive pain in these patients. According to surveyed attitudes among healthcare professionals, there was a unanimous support that patients in MCS (96%) perceive pain, whereas opinions were less clear for the VS/UWS (56%) [17]. Considering these results on varying beliefs about pain perception in DOC, physicians and healthcare workers' views on analgesia and symptom management may also be affected. Since nearly half of the surveyed doctors expressed that VS/UWS patients do not feel pain, they could be expected to act accordingly, for instance, by not providing analgesic medication in these patients during cares. How, then, are clinicians supposed to infer whether a patient in VS/UWS or MCS feels pain and that she/he may be suffering? At the patient's bedside, we are limited to evaluate the behavioural responsiveness to pain: if patients do not show signs of voluntary movement, such as to localize the source of noxious stimulus, it can be concluded they do not experience pain. Recently, the Nociception Coma Scale-Revised [18] was introduced as a more specific measure of pain in patients with DOC. However, the absence of a behavioural response cannot be taken as a proof of the absence of conscious perception [19]. As such, the inference of pain and suffering merely by observing behavioural responses may be misleading. This can be dramatically illustrated in the case of conscious but paralysed locked-in syndrome (LIS) patients, who, when in a total LIS, they are unable to use motor function to respond to painful stimulation [20]. Importantly, patients with DOC will show restricted motor reactions to noxious stimulation, either stereotyped extension denoting "decerebration" or stereotyped flexion denoting "decortication". In addition, they will frequently show increased arousal levels (evidenced by opening or widening of the eyes), quickening of breathing, increased heart rate and blood pressure or grimace-like or crying-like behaviours. As all these abilities are also seen in infants with anencephaly [21], they are considered to be of subcortical origin and not necessarily reflecting conscious perception of pain. Functional neuroimaging studies may assist in the formulation of a clearer clinical picture as regards pain perception in DOC. By means of positron emission tomography (PET), it has been shown that patients in VS/UWS exhibited cerebral processing of the incoming noxious stimulus (activation of primary somatosensory areas), but the observed neural activity was isolated and disconnected from higher-order associative brain areas which are considered necessary for conscious perception [22]. Critically, the results were very different for patients in MCS, as these patients showed cerebral activation in a more widespread network of regions similar to that of healthy controls, suggesting a potential pain perception these patients [23].

Taken together, these studies suggest that pain perception in DOC is an issue which may govern their actions. For instance, clinicians may decide not to provide

analgesic medication in VS/UWS patients during care or during the dying process after withdrawal of artificial hydration and nutrition [24], the latter on the grounds that these patients are deployed from experiencing suffering from hunger or thirst [25]. But would clinicians' views on pain perception influence their attitudes on end of life? It might be, for example, that caregivers would opt for an irreversible decision after the principle of non-maleficence (i.e. "do not harm"), to spare their patient from unnecessary suffering. According to a European survey, this does not seem to be the case. Among healthcare professions, treatment withdrawal for chronic VS/UWS was supported more (77%) when respondents considered that these patients do not feel pain [26]. Hence, it seems that clinicians made their decision according to formal guidelines on pain management in the end of life. In particular, the Multi-Society Task Force on PVS negates the possibility that patients in VS/UWS experience pain. In the same line is the Royal College of Physicians, which nevertheless recommends the administration of sedatives after treatment withdrawal, targeting at the elimination of a remote possibility of suffering [27]. According to the same survey, albeit less pronounced as compared to VS/UWS, the opinions for chronic MCS were similar: only 29% of respondents supported treatment withdrawal when they thought that these patients feel pain, and 38% considered treatment limitation options when they thought that MCS patient did not feel pain [26]. Therefore, it may be that clinicians feel more comfortable with treatment limitation options once they assure that the potential risk for pain perception is as low as possible. At the same time, it might be that respondents equalized pain perception with preserved awareness. In that respect, the potential existence of pain would give a strong reason to preserve life than opt for treatment limitation options.

Emerging Ethical Issues About End of Life

In the intensive care, medical doctors and assisting staff are confronted daily with situations where clinical decisions are critical, such as continuing or withdrawing life-sustaining treatment. Treatment limitations can be viewed as having two directions depending on whether the decision is made preoperatively or after an intervention [28]. In the former case, it may come as a refusal of cardiopulmonary resuscitation (CPR) in case of cardiopulmonary arrest. In the latter case, it most usually comes as a decision to withdraw treatment, such as the artificial respirator or artificial nutrition and hydration (ANH). CPR is almost automatically performed as an emergency therapy in order to restore heartbeat and ceased breathing, unless the patient or the legal representative has refused it in advance in a form of Do Not Resuscitate (DNR) order. Nevertheless, it should be noted that DNRs do not necessarily prohibit other therapies. They rather authorize the physician to act on this specific manner of therapy [29]. When the clinical condition of a patient has been stabilized and denoted as irreversible, decisions about ANH limitation may come into play. From a bioethical standpoint, withdrawing ANH is comparable to withdrawing mechanical ventilation, even if emotionally they may be perceived

differently. In the intensive care, the majority of deaths are the result of a medical decision to withhold or withdraw treatment [30]. Such decisions are evidence-based and rely on validated clinical or paraclinical markers of bad outcome (e.g. for anoxic coma see [31]). Despite the controversy as to whether ANH constitutes a medical treatment [32] and thus should never be withdrawn from patients [33], most of the Anglo-Saxon medical community would agree with its being a medical therapy which can be refused by patients and surrogate decision-makers [34]. Such decisions in the VS/UWS are only justified when a case is denoted as irreversible [27]. To date, guidelines with regard to temporal determination of a definitive outcome in the VS/UWS state that if no recovery is observed within 3 months after a non-traumatic or 12 months after a traumatic accident, the condition of the patient can be denoted as permanent [16].

The controversies around the clinical management at the end of life in DOC patients were reflected in a European survey ($n = 2475$), where the majority (66%) of healthcare professionals agreed to withdraw treatment from chronic VS/UWS patients, whereas only 28% agreed so for the chronic MCS [35]. Additionally, 82% of the clinicians wished not to be kept alive if they imagined themselves in a chronic VS/UWS, and a similarly high proportion (67%) agreed so if they imagined themselves in a chronic MCS [35]. Geographical region and religion were among the factors that explained most of the variance in the responses. The detected differences between the two states could be due to the existing legal ambiguity around MCS which may have influenced the surveyed participants to differentiate between expressing preferences for self versus others, by implicitly recognizing that the latter could be a step on the slippery slope to euthanasia.

Clinicians' opinions appear much more uniform with regard to brain death [36]. As mentioned earlier, the Ad Hoc Committee of the Harvard Medical School went on to the redefinition of death as a consequence of the technological advancements in the intensive care, where patients could sustain their severe injuries but maintain the function of vital organs [2]. It was, hence, possible to dissociate between cardiac, respiratory and brain functions which in turn required an alternative definition of death, moving from a cardiorespiratory towards a neurocentric formulation (i.e. irreversible coma). According to the latter, death can be viewed either as death of the whole brain or of the brainstem or as neocortical [37]. The first two are defined as the irreversible cessation of the organism as a whole, differing in their anatomical interpretation [38], whereas the last solely requires the irreversible loss of the capacity of consciousness and social interaction but has never convinced medical or legal scholars. The main utility of the introduction of brain death is that it permitted vital organ procurement for transplantation with the application of ethical restrictions, such as the dead donor rule (i.e. a patient has to be declared dead before the removal of life-sustaining organs). Based on the neocortical definition of death, however, both patients in VS/UWS and MCS can be declared dead. It has been argued that the neocortical definition is conceptually inadequate and practically unfeasible, especially in lack of a complete understanding of higher-order conscious functioning. Hence, patients with DOC are not dead [30], and organ donation options in these patients should be excluded since they violate the dead donor rule [39].

Legal Issues in Disorders of Consciousness

Disorders of consciousness have posed not only medical challenges, but in many cases they required the mediation of legal authorities in order to regulate ambiguous and controversial issues, such as end-of-life decisions. When end-of-life wishes have not been earlier formulated in the form of an advanced directive (i.e. written statement completed by a competent person in anticipation of her/his future incompetence, expressing personal treatment preferences and formal surrogacy appointment), then a surrogate decision-maker is eligible to take responsibility of the patient's clinical management. The way the legal representative should act on behalf of the patient is a progressive one: (a) the surrogate should first attempt to follow the wishes of the patient as closely as possible the way they were expressed before the accident, either orally or in the form of advance directives; (b) when the wishes are unknown and an advance directive is not available, the surrogate decision-maker should try to reproduce the patients' preferences based on their history and personal values; (c) when this is not possible, the decisions should rely on more objective markers that determine the patients' best interest (e.g. likelihood of recovery, pain management, impact on family) [28, 40]. The proxy decision-maker should mediate trying to maximize patients' self-determination and protect their interests on the principles of beneficence and non-maleficence.

The use of advance directives could also be considered as a means to regulate cost savings in the end of life. Once the wishes of a terminal patient are known, care can be taken as to constrain extraordinary means and spare the available resources on other urgent cases. However, no such rationale corresponds to the reality, and advance directives, together with hospice care and the elimination of futile care, have not contributed to the effective regulation of the economics of dying [41]. Treatment resources are not unlimited, and despite care for a good death, sometimes physicians need to do with the means they have available. The allocation of resources and the economics at the end of life have not yet been fully determined for DOC patients. In intensive care medicine, some unwritten rules can facilitate decisions as to who is to be treated, like the "first come" principle or "who will most likely benefit from the intensive care" [42]. However, for chronic DOC cases, information on resource allocation often is lacking. This may be due to the nature of chronic VS/UWS and MCS patients. These are severely brain-damaged patients for whom the dilemma on treating becomes crucial either because treatments are not guaranteed as successful (i.e. the condition is too bad to be treated) or unkind (i.e. the quality of life of those surviving is not acceptable) which may lead to an unwise way to allocate the available resources.

The legal provisions concerning the end-of-life issues in DOC differ from country to country. In the United States, where a patient-centred medical framework has been adopted, the patient is allowed to participate in the regulation of her/his own course of the disease. In the case of DOC, legal representatives in close collaboration with the clinical staff and in line with the patients' previously expressed wishes may decide together about the long-term care of irreversibly comatose patients.

There are times, however, when conflict of interests arises while making such decisions either between family and physicians, such as in the Quinlan case [43] or among family members, like the Schiavo case [44]. As most often such cases require the mediation of the court, they may have a wider publicity where the public opinion can come into play and may lead to societal movements on pro-life versus right-to-die action groups [45]. In Europe there are more subtle differences in the way treatment limitation is perceived, especially between Northern (more right-to-die oriented) and Southern European countries (more pro-life positioned) [35]. In general, decisions for treatment limitation, usually concerning ANH, need to be taken after reference to the court. Exceptions are the Netherlands, Belgium, Switzerland and Scandinavian countries where no court mediation is needed for limiting treatment in DOC patients [46].

Conclusions

Early since disorders of consciousness appeared in the clinical setting, clinicians, scholars, theologians and ethicists began to wonder what it is like to be in a state of profoundly disturbed consciousness. Are these unresponsive patients in pain, and can they even suffer from it? How can their quality of life be assessed? More importantly, is a life in such severely restricted conditions worth living? Controversies of these kinds mainly stem from how different people regard indefinite survival in disorders of consciousness. Despite the general view that quality of life is diminished in disease as a result of limited capacities to functionally engage in everyday living, these attitudes are formulated from a third-person perspective. Consequently, only rough estimations about what it is like to be in such a situation can be made. For instance, an analysis of public media reports on Terri Schiavo revealed that in some cases, the patient was described as feeling discomfort, which was incompatible with her clinical state [47]. This implies that nonmedical individuals, whose opinions are supposedly represented by media reports, may be biased towards residual cognitive function of patients with consciousness alterations. Such bias could be attributed to the fact that patients' quality of life evaluations are made from the perspective of healthy individuals who tend to underestimate patients' subjective well-being [48]. Indeed, we recently showed that patients in LIS expressed a positive subjective quality of life contrary to what could be expected in this condition [49]. As mentioned above, patients with LIS do not suffer from disorders of consciousness. As such, LIS patients constitute a nice control population for patients with disorders of consciousness due to their resemblance in terms of physical disability and possibly common history, such like LIS patients can have been in comatose-like states. Interestingly, when healthcare professionals were asked whether they wished to be kept alive if imagined themselves in this condition, 56% did not wish so despite the majority (75%) opposing to treatment withdrawal in LIS [50]. When LIS was compared to DOC, more respondents endorsed that being in a LIS was worse than being in a VS/UWS state or MCS (59%). Such studies suggest

that personal characteristics mediate opinions about DOC and LIS. The dissociation between personal preferences and general opinions underlies the difference in perspective in disability and implies that healthy persons who are not in direct contact with this patient population can have distorted pictures as to what is life in these severely constrained situations. By means of functional neuroimaging and electrophysiology, however, the grey zones of unconsciousness start getting illuminated [51]. In should be noted that although these developments are promising to detect and evaluate preserved awareness in these conditions, they need to be translated in clinical practice. For example, in terms of treatment planning, such as pain management and end-of-life decision-making, patients with disorders of consciousness are now offered the possibility to express their preferences by means of brain-computer interfaces. What remains to be clarified is the degree to which such indirect responses can be considered reliable and worthy of legal representation. Uniform ethical frameworks need to be shaped in order to guide clinicians and caregivers in terms of clinical outcome, prognosis and medical management.

References

1. Laureys S, Boly M. What is it like to be vegetative or minimally conscious? Curr Opin Neurol. 2007;20(6):609–13.
2. Ad Hoc Committee of the Harvard Medical School. A definition of irreversible coma. JAMA. 1968;205(6):337–40.
3. Zeman A. Consciousness. Brain. 2001;124:1263–89.
4. Demertzi A, Liew C, Ledoux D, Bruno MA, Sharpe M, Laureys S, et al. Dualism persists in the science of mind. Ann N Y Acad Sci. 2009;1157:1–9.
5. Posner JB, Saper CB, Schiff ND, Plum F. Plum and Posner's diagnosis of stupor and coma. 4th ed. New York: Oxford University Press; 2007.
6. Jennett B, Plum F. Persistent vegetative state after brain damage: a syndrome in search of a name. Lancet. 1972;299(7753):734–7.
7. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, León-Carrión J, Sannita WG, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 2010;8(1):68.
8. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58(3):349–53.
9. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol. 2009;9:35.
10. Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, de Los Angeles C, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. Brain. 2015;138:2619–31.
11. Sitt JD, King J, El Karoui I, Rohaut B, Faugeras F, Gramfort A, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain. 2014;137:2258–70.
12. Stender J, Gosseries O, Bruno M, Charland-verville V, Vanhaudenhuyse A, Demertzi A, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. Lancet Neurol. 2014;6736(14):8–16.

13. Casali AG, Gosseries O, Rosanova M, Boly M, Sarasso S, Casali KR, et al. A theoretically based index of consciousness independent of sensory processing and behavior. Sci Transl Med. 2013;5(198):198ra105.

14. Horne M. Are people in a persistent vegetative state conscious? Monash Bioeth Rev. 2009;28(2):12-1-12.

15. Kahane G, Savulescu J. Brain damage and the moral significance of consciousness. J Med Philos. 2009;34:6–26.

16. The Multi-society Task Force on PVS. Medical aspects of the persistent vegetative state-2. N Engl J Med. 1994;330:1572–9.

17. Demertzi A, Schnakers C, Ledoux D, Chatelle C, Bruno M-A, Vanhaudenhuyse A, et al. Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals. Prog Brain Res. 2009;177:329–38.

18. Schnakers C, Chatelle C, Vanhaudenhuyse A, Majerus S, Ledoux D, Boly M, et al. The nociception coma scale: a new tool to assess nociception in disorders of consciousness. Pain. 2010;148(2):215–9.

19. McQuillen MP. Can people who are unconscious or in the 'vegetative state' perceive pain? Issues Law Med. 1991;6(4):373–83.

20. Laureys S, Pellas F, Van Eeckhout P, Ghorbel S, Schnakers C, Perrin F, et al. The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? Prog Brain Res. 2005;150(5):495–611.

21. The infant with anencephaly. N Engl J Med. 1990;322(10):669–74.

22. Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage. 2002;17(2):732–41.

23. Boly M, Faymonville M-E, Schnakers C, Peigneux P, Lambermont B, Phillips C, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol. 2008;7(11):1013–20.

24. Fins JJ. Affirming the right to care, preserving the right to die: disorders of consciousness and neuroethics after Schiavo. Palliat Support Care. 2006;4(2):169–78.

25. Ahronheim JC, Gasner MR. The sloganism of starvation. Lancet. 1990;335(8684):278–9.

26. Demertzi A, Racine E, Bruno A, Ledoux D, Gosseries O, Vanhaudenhuyse A, et al. Pain perception in disorders of consciousness: neuroscience, clinical care, and ethics in dialogue. Neuroethics. 2013;6(1):37–50.

27. A report of a working party of the Royal College of Physicians. The vegetative state: guidance on diagnosis and management. Clin Med. 2003;3(3):249–54.

28. Bernat JL. Ethical issues in the perioperative management of neurologic patients. Neurol Clin. 2004;22:457–71.

29. Youngner SJ. Do-not-resuscitate orders: no longer secret, but still a problem. Hastings Cent Rep. 1987;17(1):24–33.

30. Laureys S. Science and society: death, unconsciousness and the brain. Nat Rev Neurosci. 2005;6(11):899–909.

31. Boveroux P, Kirsch M, Boly M, Massion P, Sadzot B, Lambermont B, et al. Evaluation du pronostic neurologique dans les encéphalopathies postanoxiques. Reanimation. 2008;17:613–7.

32. Bernat JL, Beresford HR. The controversy over artificial hydration and nutrition. Neurology. 2006;66(11):1618–9.

33. Rosner F. Why nutrition and hydration should not be withheld from patients. Chest. 1993;104(6):1892–6.

34. Steinbrook R, Lo B. Artificial feeding—solid ground, not a slippery slope. N Engl J Med. 1988;318(5):286–90.

35. Demertzi A, Ledoux D, Bruno M-A, Vanhaudenhuyse A, Gosseries O, Soddu A, et al. Attitudes towards end-of-life issues in disorders of consciousness: a European survey. J Neurol. 2011;258(6):1058–65.
36. Bernat JL. The concept and practice of brain death. Prog Brain Res. 2005;150:369–79.
37. Brierley JB, Graham DI, Adams JH, Simpsom JA. Neocortical death after cardiac arrest. A clinical, neurophysiological, and neuropathological report of two cases. Lancet. 1971;2(7724):560–5.
38. Bernat JL. Brain death. In: Laureys S, Tononi G, editors. The neurology of consciousness. 1st ed. London: Academic Press; 2009. p. 151–62.
39. Engelhardt K. Organ donation and permanent vegetative state. Lancet. 1998;351(9097):211–3.
40. Bernat JL. Clinical ethics and the law. In: Ethical issues in neurology. Lippincott Williams & Wilkins; 2002. p. 79–107.
41. Emanuel EJ, Emanuel LL. The economics of dying. The illusion of cost savings at the end of life. N Engl J Med. 1994;330(8):540–4.
42. Jennett B. Resource allocation for the severely brain-damaged. Arch Neurol. 1976;33:595–7.
43. Beresford HR. The Quinlan decision: problems and legislative alternatives. Ann Neurol. 1977;2:74–81.
44. Quill TE. Terri Schiavo—a tragedy compounded. N Engl J Med. 2005;352(16):1630–3.
45. Wijdicks EFM. Law and bioethics. In: The comatose patient. New York: Oxford University Press; 2008. p. 201–16.
46. Jennett B. Ethical issues. In: The vegetative state: medical facts, ethical and legal dilemmas. Cambridge: Cambridge University Press; 2002. p. 97–125.
47. Racine E, Amaram R, Seidler M, Karczewska M, Illes J. Media coverage of the persistent vegetative state and end-of-life-decision-making. Neurology. 2008;71(13):1027–32.
48. Nizzi M-C, Demertzi A, Gosseries O, Bruno M-A, Jouen F, Laureys S. From armchair to wheelchair: how patients with a locked-in syndrome integrate bodily changes in experienced identity. Conscious Cogn. 2012;21(1):431–7.
49. Bruno M-A, Bernheim JL, Ledoux D, Pellas F, Demertzi A, Laureys S. A survey on self-assessed well-being in a cohort of chronic locked-in syndrome patients: happy majority, miserable minority. BMJ Open. 2011;1(1):e000039.
50. Demertzi A, Jox RJ, Racine E, Laureys S. A European survey on attitudes towards pain and end-of-life issues in locked-in syndrome. Brain Inj. 2014;28(9):1209–15.
51. Demertzi A, Laureys S. Detecting levels of consciousness. In: Clausen J, Levy N, editors. Handbook of neuroethics. Dordrecht: Springer; 2015. p. 665–77.