

IS ORAL FEEDING COMPATIBLE WITH AN UNRESPONSIVE WAKEFULNESS SYNDROME?

Evelyne Mélotte^{1,2}, Audrey Maudoux^{2,3}, Sabrina Delhalle³, Charlotte Martial², Georgios Antonopoulos², Stephen Karl Larroque², Sarah Wannez², Marie-Elisabeth Faymonville⁴, Jean-François Kaux¹, Steven Laureys², Olivia Gosseries², Audrey Vanhaudenhuyse^{2,4}

¹*Physical and Rehabilitation Medicine Department, University Hospital of Liege, Liège, Belgium*

²*GIGA Consciousness, Coma Science Group and Neurology Department, University and University Hospital of Liege, Liège, Belgium*

³*Otorhinolaryngology Head and Neck Surgery Department, University and University Hospital of Liege, Liège, Belgium*

⁴*Hypnosis and Pain GIGA Center and Algology and Palliative Care Department, University and University Hospital of Liege, Liège, Belgium*

Keywords:

Swallowing, Dysphagia, Oral-feeding, Consciousness, Unresponsive wakefulness syndrome

Abstract

Objective The aim of the study is to explore the possibility of oral feeding in unresponsive wakefulness syndrome/vegetative state (UWS/VS) patients.

Method We reviewed the clinical information of 68 UWS/VS patients (mean age 45 ± 11 ; range 16–79 years) searching for mention of oral feeding. UWS/VS diagnosis was made after repeated behavioural assessments using the Coma Recovery Scale—Revised. Patients also had complementary neuroimaging evaluations (positron emission tomography, functional magnetic resonance imaging and electroencephalography and diffusion tensor imaging).

Results Out of the 68 UWS/VS patients, only two could resume oral feeding (3%). The first patient had oral feeding (only liquid and semi liquid) in addition to gastrostomy feeding and the second one could achieve full oral feeding (liquid and mixed solid food). Clinical assessments concluded that they fulfilled the criteria for a diagnosis of UWS/VS. Results from neuroimaging and neurophysiology were typical for the first patient with regard to the diagnosis of UWS/VS but atypical for the second patient.

Conclusion Oral feeding that implies a full and complex oral phase could probably be considered as a sign of consciousness. However, we actually do not know which components are necessary to consider the swallowing conscious as compared to reflex. We also discussed the importance of swallowing assessment and management in all patients with altered state of consciousness.

Background

The unresponsive wakefulness syndrome (UWS/VS) is a disorder of consciousness characterized by the presence of eye-opening and reflexive movements, without conscious behaviours [1]. In patients with UWS/VS, cortical white and grey matters are severely affected [2]. Fluorodeoxyglucose positron emission tomography (FDG-PET) studies show impairment of metabolism in the polymodal associative cortices but relatively preserved metabolism in the brainstem [3, 4]. Swallowing is a complex sensorimotor function which is either initiated voluntarily or occurs spontaneously (reflex swallowing). Each type of swallowing activates different cortical regions. Neuroimaging studies demonstrated that while the central pattern generator (CPG; localized in the brainstem) mediates the reflexive component of swallowing, many cortical regions are involved in voluntary as well as in reflex swallowing [5–8]. However, even if both forms of swallowing involve cortical regions activation, the network of brain regions activated during reflexive swallowing is different from that observed during volitional swallowing [5–8]. More specifically, fMRI studies in healthy volunteers showed that cerebral cortical representation of saliva and water reflexive swallow mainly involved bilateral primary sensorimotor cortices and insular cortices [5, 7]. On the other hand, during saliva and water bolus volitional swallows, there is an activation of the primary sensorimotor, premotor, prefrontal, frontal opercular, temporal and insular cortices, anterior cingulate gyrus and precuneus with a most consistent cortical activation in the primary sensorimotor cortex [5, 7, 8]. In the case of UWS/VS, patients classically receive hydration and nutrition through an enteral feeding tube. The possibility of resuming oral feeding in the UWS/VS population is greatly debated [2, 9–12], and it is actually unclear if the presence of oral feeding is compatible with the diagnosis of UWS/VS or if this observation should lead to a modification of diagnosis (i.e. minimally conscious state). In this article, we document the feasibility of oral feeding in patients with UWS/VS.

Method

We retrospectively reviewed the clinical information of 68 chronic patients in UWS/VS. These patients were sent by their institution, doctor or family to be hospitalized for a 1-week multimodal assessment in the University Hospital of Liège. From December 2006 to May 2017, 68 chronic patients in UWS/VS underwent this hospitalization week. The inclusion criteria were a chronic state (> 3 months after onset) and a diagnosis of UWS/VS. Diagnosis of UWS/VS was made after repeated behavioural assessments by trained and experienced neuropsychologists using the Coma Recovery Scale—Revised (CRS-R, [13]). The CRS-R consists of six subscales (auditory, visual, motor, and oromotor functions as well as communication and arousal) giving us 23 items ordered by degree of complexity, ranging from reflexive to cognitively mediated behaviours.

We also performed complementary clinical neuroimaging assessments. FDG-PET data were normalized to signal intensity of the skin [14]. The mean value of skin voxels was selected as intensity scaling index for each volume. The skin was chosen due to the fact that it is not affected by the brain injury and metabolic activity can easily be extracted. For resting state functional Magnetic Resonance Imaging (fMRI), spontaneous BOLD signal correlations were measured between different brain regions for the

default mode, auditory, visual, sensorimotor, salience and frontoparietal networks [15]. We also used diffusion tensor imaging (DTI) to quantify the orientation and directional uniformity of water diffusion in brain tissue [16]. Finally, clinical electroencephalograms (EEG) using 19 electrodes were also acquired and interpreted by a certified neurologist. Among the 68 patients in UWS/Vs (mean age 45 ± 11 ; range 16–79 years), etiology was traumatic in 17 cases and non-traumatic in 51 cases [anoxic encephalopathy ($n = 34$), ischemic or hemorrhagic stroke ($n = 8$), mixed etiology ($n = 4$), others ($n = 5$)]. Median interval since insult was 30 months (Q1 = 9 and Q3 = 39).

Results

Out of the 68 UWS/Vs patients included in this study, according to the medical records and the questionnaires fulfilled by the family, the doctor and the nurses, only two patients could resume oral feeding (3%). The first patient received oral feeding (i.e. liquid and semi liquid) in addition to gastrostomy feeding, with a functional swallowing based on an otorhinolaryngological examination, and the second patient had full oral feeding (i.e. liquid and mixed solid food).

Case report 1

MEDICAL HISTORY

A 17-year-old man was admitted to intensive care unit after an ethylic coma complicated by a pneumopathy caused by gastric liquid inhalation. The situation was evolving positively, allowing the patient to leave the hospital after a few days. However, a couple of days after the discharge, the patient suffered from a cardiorespiratory arrest occurring after an effort at home. Cardiorespiratory resuscitation was performed and ventilation was needed. An unconscious state was observed with a lack of evolution. One month later, the patient was discharged from intensive care unit with a diagnosis of UWS/Vs and returned to his parent's home without any period in a rehabilitation centre. He received nurse care each day and physical therapy thrice a week but no swallowing care. Fourteen years after the brain injury, he came to the University Hospital of Liège. He was still considered as UWS/Vs.

ORAL FEEDING

When the patient came at the University Hospital of Liège, he was entirely fed by mouth with thick to thin liquid texture (corresponding to level 0–4 in the International Dysphagia Diet Standardisation Initiative—IDDSI Framework [17]). However, the patient still had the gastrostomy tube for complementary nutrition of about 0.5 l per day.

Otorhinolaryngological exam were performed. The fiberoptic endoscopic evaluation showed preserved laryngeal mobility and cough reflex, as well as no salivary or secretions stasis. Semi-liquid and liquid test was performed. For semi-liquid, the patient could open his mouth when the spoon

touched his lips but he was not able to close it around the spoon. Antero-posterior movements of the tongue were observed and there was no buccal stasis. The initiation of swallowing reflex was delayed but no inhalation occurred. Liquid was given with a syringe on lingual basis. A posterior leakage was observed, the initiation of swallowing reflex was delayed but ventricular bands close to protect the larynx and no inhalation occurred.

MULTIMODAL DIAGNOSIS ASSESSMENT

CRS-R total scores ranged from 4 to 7 depending on the day (total of 6 evaluations). The patient showed spontaneous eye opening, head and legs movements, auditory startle reflex, no response to command, no visual fixation, no visual pursuit, bilateral abnormal flexion in response to noxious stimulations, oral reflex movements and vocal productions but no communication. The total CRS-R score on the day of the otorhinolaryngological exam was 5. Clinical assessments concluded that he fulfilled the criteria for a diagnosis of UWS/VS. Neuroimaging results also pointed in that direction (**Fig. 1a–h**). FDG-PET showed a drop in brain metabolism of 79% as compared to healthy controls, with hypometabolism in the global lateral and medial fronto-parietal network and a preservation of the brainstem and cerebellum (**Fig. 1a, b**). MRI revealed a global bilateral atrophy of the cerebral and cerebellar hemispheres (**Fig. 1c, d**). fMRI showed no spontaneous brain activity in the different resting state networks (**Fig. 1c–f**). DTI showed diffuse alteration of white matter connections (**Fig. 1g, h**). Clinical electroencephalograms (EEG) suggested a severe encephalopathy.

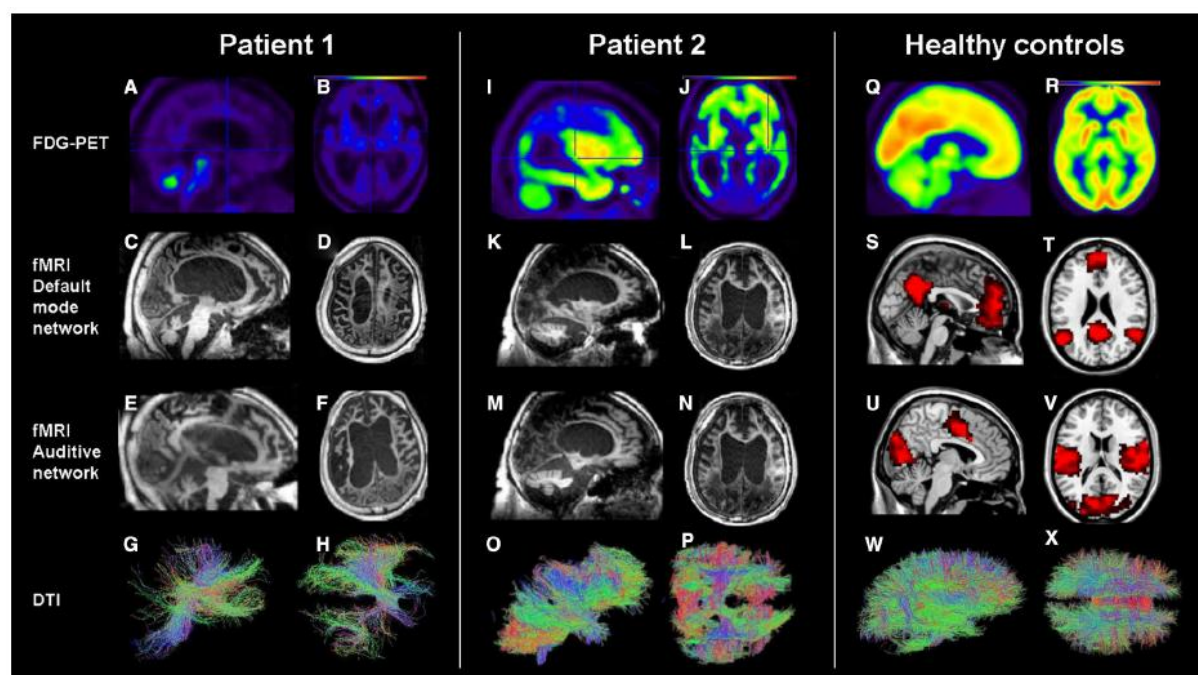


Fig. 1 Neuroimaging results (PET, fMRI default mode network, fMRI auditory network and DTI) of the two patients and healthy controls. Patient 1 (left panel): FDG-PET showed a drop in brain metabolism of 79% with hypometabolism in the global lateral and medial fronto-parietal network and a preservation of the brainstem and cerebellum (**a, b**). MRI revealed a global bilateral atrophy of the cerebral and cerebellar hemisphere in patient 1 (**c, d**). DTI showed diffuse alteration of white matter connections (**g, h**). Patient 2 (central panel): drop in brain metabolism of 47% with hypometabolism in the bilateral parieto-temporal associative areas but relative preservation of the brainstem, cerebellum and frontal and occipital cortex (**i, j**). MRI

revealed a global cerebellar vermis atrophy, a mesencephalic bilateral atrophy, a parieto-occipital cortex and basal ganglia (principally left thalamic) atrophy (**k**, **l**). DTI showed loss of white matter in dorsal posterior area bilaterally and disorganisation of fibers in parietal cortex (**o**, **p**). In fMRI, performed with sedation, patient 1 and 2 showed no spontaneous brain activity in the different resting state networks (**c–f** and **k–n**, respectively)

Case report 2

MEDICAL HISTORY

A 35-year-old man was admitted to the hospital as a result of a motor road accident (moped knocked down by a car). There was no loss of awareness or neurologic symptoms but some fractures in the hand and kneecap. Three days later, he was admitted to the intensive care unit after a cardiac arrest during a kneecap surgery. He sustained an anoxic brain injury and remained comatose during the following 10 weeks. He then recovered spontaneous eye opening and startle reflexes to loud sound and bright light. Three weeks after the brain injury, computed tomography revealed cerebral collapse on basal ganglia. He was tracheostomized during the first three months then oral feeding was gradually started. At the discharge, neurological examination retained the diagnosis of “permanent vegetative state” based on the absence of any behavioural sign of consciousness. The patient returned back home 4 months after the anoxic brain injury with a naso-gastric tube feeding. Nineteen years after the insult, the patient came to the University Hospital of Liège for a multimodal diagnosis assessment.

ORAL FEEDING

Oral liquid and solid food feeding were gradually continued by the mother after the initial hospitalization and enteral feeding was stopped 2 weeks after the discharge. The patient never received swallowing therapy. When he came to our center, the patient was entirely fed by mouth. He also orally received hydration and medications. Solid food corresponded to level 5 (minced and moist) in the IDDSI Framework [17]. Three meals per day were administrated by the mother or the nurse with normal utensils. The patient opened his mouth when the spoon was touching his lips but was not able to close his lips around the spoon. There was no history of lung infection and his body weight was stable. The nutritional status measured by albumin indicator was normal (43gr/L norms 38–49).

MULTIMODAL DIAGNOSIS ASSESSMENT

Behavioural examinations confirmed the diagnosis of UWS/ VS. The CRS-R total scores ranged from 6 to 7 depending on the day (total of 6 evaluations) and showed spontaneous eyes opening, auditory startle reflex, no response to command, no visual fixation or pursuit, no blink to threat, bilateral flexion responses to noxious stimulations, oral reflex movements and vocalizations without any communication. However, neuroimaging examinations (FDG-PET, DTI and EEG) looked atypical. FDG-PET showed a drop in brain metabolism of 47% as compared to healthy controls with relative metabolic preservation of the brainstem, cerebellum, frontal and occipital cortices and hypometabolism in the bilateral parieto-temporal associative areas (**Fig. 1i**, **j**). MRI revealed global cerebellar vermis atrophy, mesencephalic bilateral atrophy, parieto-occipital cortex and basal ganglia (principally left thalamic)

atrophy. There was also a hyperintense signal in the midbrain and the pons compatible with a Wallerian degeneration. A quadriventricular dilatation was also noted as well as bilateral white matter diffuse lesions encompassing parietal and cingulate posterior cortices and precuneus (**Fig. 1k, l**). fMRI showed no spontaneous brain activity in any of the resting state networks (**Fig. 1k–n**). DTI showed a loss of white matter in dorsal posterior area bilaterally and disorganisation of fibers in parietal cortex (**Fig. 1o, p**). EEG depicted symmetrical reactive slow theta activity, suggesting of a medium and diffuse cerebral suffering.

Discussion

In our population, only two out of 68 patients in UWS/VS could safely resume oral feeding. This is thus a rare observation (3%) among patients in UWS/VS. We see that the period between the accident and the assessment in our center is very long. It reflects the failure of most health care system to adequately care for disorders of consciousness patients after the acute phase. A previous retrospective study showed that in 260 patients diagnosed as “permanent vegetative state”, 8% could perform oral feeding [18]. However, no information was given about how the diagnosis of UWS/VS was made and if standardized behavioural assessments were used. Indeed, repeated behavioural assessment is essential to make a proper diagnosis. A recent study show that performing a single CRS-R assessment could lead to up to 35% of misdiagnosed UWS/VS [19]. In our study, repeated clinical assessments ($n = 6$) matched with the diagnosis of UWS/VS in both patients according to actual behavioral diagnosis criteria. For patient 1, neuroimaging results are in line with the UWS/VS diagnosis. However, atypical results were observed for patient 2 (relative metabolic preservation of frontal and occipital cortices, relatively preserved DTI and theta activity but no spontaneous resting state fMRI networks). Given the dissociation between the behaviour and the neuroimaging findings, patient 2 could be considered as being in a functional locked-in [20, 21] or in a MCS* [22, 23], or even maybe in a state of cognitive motor dissociation [24]. However, advanced diagnostic techniques during a swallowing task or by means of mental imagery tasks should be performed to confirm this alternative diagnosis. Considering that the diagnosis of UWS/VS implies the absence of any voluntary behaviour, the observation of functional swallowing in these two patients raises many questions and reflexions.

As we described above, swallowing can either occurs spontaneously (reflex swallowing) or be initiated voluntary (for a review see [25]). Reflex swallowing is classically described as an irrepressible swallowing movement occurring despite the intention to avoid swallowing, without volitional input for initiation [5] and without conscious control [25]. Reflex swallowing is classically assessed with injection of minute amounts of water directly into the pharynx [5] or “naïve” saliva swallow [7]. According to the classical view of the initiation of reflex swallow, the oral phase is bypassed. Reflex swallowing is observed as early as the 12th gestational week, before the cortical and subcortical structures have totally developed [26]. It has also been reported that swallowing can be observed in the human anencephalic foetus [27, 28]. On the other hand, voluntary swallowing corresponds to sequential eating or drinking voluntarily initiated or facilitated by the cerebral cortex [25]. Materials in the mouth (food or saliva) and the cortical drive to the tongue and the submental muscles are necessary for initiation of voluntary swallowing [25]. In voluntary swallowing studies, water or food was injected in

the mouth without any verbal instruction to swallow [7, 8] or subjects were cued to swallow volitionally their saliva [5, 7].

As described in the introduction, the network of brain regions activated during reflexive swallowing is different from that observed during volitional swallowing [5–8, 29, 30]. In previous studies, voluntary and reflex swallow can be differentiated in terms of state of awareness, wakefulness, and to what extent the oral phase is involved [5–8, 25]. However, because swallowing was never studied in disorders of consciousness (DOC) population, we actually do not know what is sufficient to consider swallowing as conscious compared to reflex swallowing in this population of patients. In terms of the oral phase of the swallowing, are lip closure, mastication, tongue manipulation and propulsion necessary to consider swallowing a conscious action? This issue is still debated and future studies are needed to define what is a “conscious” swallowing and what is a reflex swallowing in DOC patients. Given the retrospective character of this study, we are not able to analyze precisely the efficacy of the oral phase. However, we can make prediction by looking at the food texture that these two patients received. The first patient was able to swallow liquid and semi-liquid textures, which does not necessarily imply a complex oral phase. On the other hand, patient 2 received solid food and this type of texture definitely implies some form of functional oral phase to propel the food. We can then consider that the swallowing of patient 2 probably reflects higher level of conscious swallowing than the swallowing of patient 1. Interestingly, these observations are in line with the atypical neuroimaging results found in patient 2. Furthermore, given that voluntary swallowing is initiated or facilitated by the cerebral cortex, we can suppose that the preservation of some cortical areas (principally in the frontal cortex) in patient 2 can contribute to better swallowing results. However, based on the current neuroimaging results, we should be careful in saying that swallowing is reflex or conscious. This precise information can only be obtained with functional imaging performed during swallowing.

The swallowing abilities of the patients with DOC should be systematically assessed and compared among the different states of consciousness. This is critical as misdiagnosis can have serious medical and ethical consequences for the patients and their family. Indeed, prognosis, treatment decisions (particularly pain treatment) and medico-legal judgements (especially end-of-life decision-making) are influenced by the diagnosis [31, 32].

Neuropathological studies seem to indicate that a correlation exists between the level of consciousness and swallowing function: the higher the cognitive function, the better the chance to achieve oral feeding [33–36]. Based on this, the atypical brain activation observed in patient 2 in addition to his capacity to perform full oral feeding should prompt us to be more careful and rethink our initial clinical UWS/ VS diagnosis.

Finally, this case study emphasizes the importance of systematic observations of swallowing capacities in all patients with altered consciousness. Indeed, as shown in our study, even patients with no evident sign of consciousness can sometimes demonstrate some functional swallowing. More than 30 years ago, it was demonstrated that some assessments (pre-feeding assessment and functional assessment) could be performed in severe head-injured patients [34]. Since then, other studies showed that objective swallowing assessments [realized with instrumental assessments such as fiberoptic endoscopic exam (FEES) or videofluoroscopy (VFSS)] could be performed safely in patients regardless their level of consciousness [37–39]. Brady et al. [38] considered that the decision to introduce oral

food or liquid in DOC patients should only be made after the completion of an objective swallowing evaluation. We share Brady's opinion and we insist on the importance of the realization of a systematic swallowing evaluation including instrumental assessments of swallowing such as VFSS or FEES, as they are the only reliable way to identify silent aspiration due to poor cough reflex [40]. Combined to VFSS or FEES, swallowing function clinical evaluation will give complementary information on the pre-swallowing and swallowing abilities [38, 39].

Clinicians working with DOC patients are also faced with the challenge of providing meaningful therapy. Safety and treatment efficacy of swallowing rehabilitation in patients with DOC is still debated [33, 37, 38] (for a review see [41]). Some clinicians advocate providing patients with a level II (generalized responses/vegetative state) or III (localized responses/minimally conscious) in Ranchos Los Amigos Scale (RLAS [42]) with food/liquid presentations for taste stimulation [33]. Other clinicians recommend no oral feedings until the patient's level of consciousness improves beyond level III in RLAS [34, 38, 43]. However, based on our observations, a few patients who do not show conscious behaviour according to the CRS-R can perform oral feeding even if the majority of DOC patients are fed with enteral feeding. Thus, we believe that the decision to introduce food or liquid should not rely uniquely on the observation of conscious behaviour but rather on performance observed during an objective swallowing assessment.

Several limitations of the study should be taken into account.

First, we have considered only patients who were known to be fed at the moment of their admission for the one-week multimodal assessment. This introduces a bias in our data given that we might have missed patients who can potentially be fed orally but who are not (due for example to the lack of stimulation, fear of bronchoinhalation, etc.). However, we think that this number of missed patients is probably low. In our experience, almost all families try to reintroduce oral feeding. Most of the time they are confronted to difficult situations making it impossible. This is namely the hypercontraction of masseter or bite reflex reducing considerably the chance of oral feeding, the total absence of oro-facial reaction when trying to put some food in the mouth, the absence of swallowing reflex, etc. When these difficulties are not present, further testing is usually undertaken and if judged safe, oral feeding is pursued. Therefore, the number of patients that were not fed at the moment of their admission but could have had full oral feeding is probably very low. Second, as we described before, it has been more informative if we had swallowing assessment with standardized otorhinolaryngological techniques for all UWS/VS patients. Further studies are needed to better estimate rate and characteristics of swallowing in these DOC patients. Finally, we cannot totally exclude that the absence of response on resting state fMRI in our two patients is not due to the administration of sedation during the scanning. However, this was a light sedation (0.8 mg/mL) done mainly to improve the patients' comfort in the scanner. Moreover, a recent study demonstrated that connectivity decreases due to propofol sedation are relatively small compared to those already caused by structural brain injury [44]. Another recent study also showed that administration of sedation did not prevent some patients with DOC to show fMRI responses during active imagery tasks [45].

Conclusion

Oral feeding in UWS/VS patients is rare. We here presented the case of two patients who could achieve oral feeding. Although the diagnosis based on clinical behavioural assessment suggests an UWS/VS, we found some atypical neuroimaging results in the second patient who performed full oral feeding. Resuming full oral feeding may be related to recovery of some brain functions, which probably lead to a higher level of consciousness than UWS/VS. Full oral feeding could thus potentially be considered as a sign of consciousness. However, further studies will have to explore more precisely if functional swallowing is really a sign of consciousness and if this observation can be another key element to determine the diagnosis. We suggest that only the recovery of a full and complex oral phase (including solid food) should be considered as a sign of consciousness. Indeed, in some UWS/VS patients, the rare recovery of oral feeding with liquid and semi-liquid textures could be due to the presence of reflex swallowing rather than conscious swallowing.

A systematic swallowing assessment should be performed in all DOC patients regardless of their level of consciousness. This will allow to better tract residual swallowing function in DOC patients and see if it can be related to the level of consciousness. Various therapeutic techniques should be assessed and therapeutical objectives/purposes should be developed. Finally, we would like to emphasize that in these two patients the presence of relatively preserved swallowing function does not seem to predict good prognostic in terms of functional outcomes given their long history of chronic UWS/VS condition.

Acknowledgements

The study was supported by the University and University Hospital of Liège, the French Speaking Community Concerted Research Action (ARC 12-17/01), the Belgian National Funds for Scientific Research (FRS-FNRS), Human Brain Project (EU-H2020-fetflagship-hbp-sga1-ga720270), Luminous project (EUH2020-fetopen-ga686764), the Wallonie-Bruxelles International, the James McDonnell Foundation, Mind Science Foundation, IAP research network P7/06 of the Belgian Government (Belgian Science Policy), the European Commission, the Public Utility Foundation 'Université Européenne du Travail', "Fondazione Europea di Ricerca Biomedica", the Bial Foundation, Belgian National *Plan Cancer* (139). OG and AM are post-doctoral fellows, and SL is research director at FRS-FNRS. We thank Pr Pierre Maquet from the Neurology department, University Hospital of Liège, as well as the whole Neurology staff, patients, and their families.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ethics Committee of the Medical School of the University of Liège and written consents were obtained from the legal representative of each patient.

References

1. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, León-Carrión J, Sannita WG et al (2010) Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. *BMC Med* 8:68. <https://doi.org/10.1186/1741-7015-8-68>
2. Royal College of Physicians (2003) The vegetative state: guidance on diagnosis and management. *Clin Med* 3:249–254. <https://doi.org/10.7861/clinmedicine.3-3-249>
3. Laureys S, Goldman S, Phillips C, Van Bogaert P, Aerts J, Luxen A et al (1999) Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. *Neuroimage* 2:377–382. <https://doi.org/10.1006/nimg.1998.0414>
4. Laureys S (2004) Functional neuroimaging in the vegetative state. *NeuroRehabilitation* 19:335–341. <https://doi.org/10.1016/j.apmr.2006.07.272>
5. Kern MK, Jaradeh S, Arndorfer RC, Shaker R (2001) Cerebral cortical representation of reflexive and volitional swallowing in humans. *Am J Physiol Gastrointest Liver Physiol* 280:G354–G360. <https://doi.org/10.1152/ajpgi.2001.280.3.G354>
6. Ertekin C, Aydogdu I (2003) Neurophysiology of swallowing. *Clin Neurophysiol* 114:2226–2244. [https://doi.org/10.1016/S1388-2457\(03\)00237-2](https://doi.org/10.1016/S1388-2457(03)00237-2)
7. Martin RE, Goodyear BG, Gati JS, Menon RS (2001) Cerebral cortical representation of automatic and volitional swallowing in humans. *J Neurophysiol* 85:938–950. <https://doi.org/10.1152/jn.2001.85.2.938>
8. Hamdy S, Mikulis DJ, Crawley A et al (1999) Cortical activation during human volitional swallowing: an event-related fMRI study. *Am J Physiol* 277:219–225. <https://doi.org/10.1152/ajpgi.1999.277.1.G219>
9. The Multi-Society Task Force on PVS (1994) Medical aspects of the persistent vegetative state (2). *N Engl J Med* 330:1572–1579. <https://doi.org/10.1056/NEJM199406023302206>
10. Australian Government National Health and Medical Research Council (2003) Post-Coma Unresponsiveness (Vegetative State): a clinical framework for diagnosis. An information paper. Australian Government National Health and Medical Research Council
11. ANA (1993) Persistent vegetative state: report of the American Neurological Association Committee on Ethical Affairs. *Ann Neurol* 33:386–390. <https://doi.org/10.1002/ana.41033.0409>
12. Bernat J (1992) The boundaries of the persistent vegetative state. *J Clin Ethics* 3:176–180
13. Giacino JT, Kalmar K, Whyte J (2004) The JFK Coma recovery scale-revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 85:2020–2029. <https://doi.org/10.1016/j.apmr.2004.02.033>
14. Stender J, Mortensen KN, Thibaut A, Darkner S, Laureys S, Gjedde A et al (2016) The minimal energetic requirement of sustained awareness after brain injury. *Curr Biol* 26:1494–1499. <https://doi.org/10.1016/j.cub.2016.04.024>
15. Demertzi A, Gómez F, Crone JS, Vanhaudenhuyse A, Tshibanda L, Noirhomme Q et al (2014) Multiple fMRI system-level baseline connectivity is disrupted in patients with consciousness alterations. *Cortex* 52:35–46. <https://doi.org/10.1016/j.cortex.2013.11.005>
16. Gomez F, Soddu A, Noirhomme Q, Vanhaudenhuyse A, Tshibanda L, Lepore N, et al (2012) DTI based structural damage characterization for Disorders of Consciousness. *Proceedings International Conference on Image Processing ICIP*, pp 1257–1260. <https://doi.org/10.1109/icip.2012.6467095>
17. Cichero JAY, Lam P, Steele CM, Hanson B, Chen J, Dantas RO et al (2016) Development of international terminology and definitions for texture-modified foods and thickened fluids used in dysphagia management: the IDDSI framework. *Dysphagia* 32:1–22. <https://doi.org/10.1007/s00455-016-9758-y>
18. Lin L-C, Hsieh P-C, Wu S-C (2008) Prevalence and associated factors of pneumonia in patients with vegetative state in Taiwan. *J Clin Nurs* 17:861–868. <https://doi.org/10.1111/j.1365-2702.2006.01883>
19. Wannez S, Heine L, Thonnard M, Gosseries O, Laureys S (2017) The repetition of behavioral assessments in diagnosis of disorders of consciousness. *Ann Neurol* 81:883–889. <https://doi.org/10.1002/ana.24962>
20. Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S (2011) From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *J Neurol* 258:1373–1384. <https://doi.org/10.1007/s00415-011-6114-x>
21. Formisano R, D'Ippolito M, Catani S (2013) Functional locked-in syndrome as recovery phase of vegetative state. *Brain Inj* 27:1332. <https://doi.org/10.1007/s00415-011-6114-x>
22. Gosseries O, Zasler ND, Laureys S (2014) Recent advances in disorders of consciousness: focus on the diagnosis. *Brain Inj* 28:1141–1150. <https://doi.org/10.3109/02699052.2014.920522>
23. Bodart O, Gosseries O, Wannez S, Thibaut A, Annen J, Boly M, Rosanova M, Casali AG, Casarotto S, Tononi G, Massimini M, Laureys S (2017) Measures of metabolism and complexity in the brain of patients with disorders of consciousness. *Neuroimage Clin* 6(14):354–362. <https://doi.org/10.1016/j.nicl.2017.02.002>
24. Schiff ND (2015) Cognitive motor dissociation following severe brain injuries. *JAMA Neurol* 72:1413–1415. <https://doi.org/10.1001/jamaneurol.2015.2899>
25. Ertekin C (2011) Voluntary versus spontaneous swallowing in man. *Dysphagia* 26:183–192. <https://doi.org/10.1007/s00455-010-9319-8>
26. Jean A (2001) Brain stem control of swallowing: neuronal network and cellular mechanisms. *Physiol Rev* 81:929–969. <https://doi.org/10.1002/cne.902830207>

27. Peleg D, Goldman JA (1978) Fetal deglutition: a study of the anencephalic fetus. *Eur J Obstet Gynecol Reprod Biol* 8:133–136
28. Pritchard A (1965) Deglutition by normal and anencephalic fetuses. *Obstet Gynecol* 25:289–297
29. Mosier KM, Liu W-C, Maldjian JA, Shah R, Modi B (1999) Lateralization of cortical function in swallowing: a functional MR imaging study. *Am J Neuroradiol* 20:1520–1526
30. Zald D, Pardo J (1999) The functional neuroanatomy of voluntary swallowing. *Ann Neurol* 46:281–286. <https://doi.org/10.1016/j.plev.2009.06.001>
31. Bernat J (2008) Ethical issues in the management of patients with impaired consciousness. In: Young GB, Wijdicks EFM (eds) *Handbook of clinical neurology*, 90th edn. Elsevier, Paris, p 369–382
32. Demertzi A, Ledoux D, Bruno MA, Vanhaudenhuyse A, Gosseries O, Soddu A, Schnakers C, Moonen G, Laureys S (2011) Attitudes towards end-of-life issues in disorders of consciousness: a European survey. *J Neurol* 258:1058–1065. <https://doi.org/10.1007/s00415-010-5882-z>
33. Mackay LE, Morgan AS, Bernstein BA (1999) Swallowing disorders in severe brain injury: risk factors affecting return to oral intake. *Arch Phys Med Rehabil* 80:365–371
34. Winstein CJ (1983) Neurogenic dysphagia. Frequency, progression, and outcome in adults following head injury. *Phys Ther* 63:1992–1997
35. Formisano R, Voogt RD, Buzzi MG, Vinicola V, Penta F, Peppe A et al (2004) Time interval of oral feeding recovery as a prognostic factor in severe traumatic brain injury. *Brain Inj* 18:103–109. <https://doi.org/10.1080/0269905031000149470>
36. Hansen TS, Engberg AW, Larsen K (2008) Functional oral intake and time to reach unrestricted dieting for patients with traumatic brain injury. *Arch Phys Med Rehabil* 89:1556–1562. <https://doi.org/10.1016/j.apmr.2007.11.063>
37. O'Neil-Pirozzi TM, Momose KJ, Mello J, Lepak P, McCabe M, Connors JJ et al (2003) Feasibility of swallowing interventions for tracheostomized individuals with severely disordered consciousness following traumatic brain injury. *Brain Inj* 17:389–399. <https://doi.org/10.1080/0269905031000070251>
38. Brady SL, Darragh M, Escobar N, O'Neil K, Pape T, Rao N (2006) Persons with disorders of consciousness: are oral feedings safe/effective? *Brain Inj* 20:1329–1334. <https://doi.org/10.1080/02699050601111435>
39. Bremare A, Rapin A, Veber B, Beuret-Blanquart F, Verin E (2016) Swallowing disorders in severe brain injury in the arousal phase. *Dysphagia* 31:511–520. <https://doi.org/10.1007/s00455-016-9707-9>
40. Miles A, Zeng ISL, McLauchlan H, Huckabee M-L (2013) Cough reflex testing in dysphagia following stroke: a randomized controlled trial. *J Clin Med Res* 5:222–233. <https://doi.org/10.4021/jocmr1340w>
41. Maudoux A, Breuskin I, Gosseries O, Melotte E, Schnakers C, Vanhaudenhuyse A (2017) Feasibility of oral feeding in patients with disorders of consciousness. In: Schnakers C, Laureys S (eds) *Coma and disorders of consciousness*, 2nd edn. Springer, New York
42. Hagen C, Malkmus D, Durham P (1979) Levels of cognitive functioning, rehabilitation of the head injured adult; comprehensive physical management, Downey. Professional Staff Association of Rancho Los Amigos National Rehabilitation Center, Downey
43. De Tanti A, Zampolini M, Pregno S (2015) Recommendations for clinical practice and research in severe brain injury in intensive rehabilitation: the Italian Consensus Conference. *Eur J Phys Rehabil Med* 51:89–103
44. Kirsch M, Guldenmund P, Bahri MA, Demertzi A, Baquero K, Heine L et al (2017) Sedation of patients with disorders of consciousness during neuroimaging: effects on resting state functional brain connectivity. *Anesth Analg* 124:588–598. <https://doi.org/10.1213/ANE.0000000000001721>
45. Bodien YB, Giacino JT, Edlow BT (2017) Functional MRI motor imagery tasks to detect command following in traumatic disorders of consciousness. *Front Neurol* 8:688. <https://doi.org/10.3389/fneur.2017.00688>