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Deep brain stimulation for the early treatment of the minimally conscious state and vegetative state: experience in 14 patients

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OBJECTIVE An effective treatment of patients in a minimally conscious state (MCS) or vegetative state (VS) caused by hypoxic encephalopathy or traumatic brain injury (TBI) is not yet available. Deep brain stimulation (DBS) of the thalamic reticular nuclei has been attempted as a therapeutic procedure mainly in patients with TBI. The purpose of this study was to investigate the therapeutic use of DBS for patients in VS or MCS.

METHODS Fourteen of 49 patients in VS or MCS qualified for inclusion in this study and underwent DBS. Of these 14 patients, 4 were in MCS and 10 were in VS. The etiology of VS or MCS was TBI in 4 cases and hypoxic encephalopathy due to cardiac arrest in 10. The selection criteria for DBS, evaluating the status of the cerebral cortex and thalamocortical reticular formation, included: neurological evaluation, electrophysiological evaluation, and the results of positron emission tomography (PET) and MRI examinations. The target for DBS was the centromedian-parafascicular (CM-pf) complex. The duration of follow-up ranged from 38 to 60 months.

RESULTS Two MCS patients regained consciousness and regained their ability to walk, speak fluently, and live independently. One MCS patient reached the level of consciousness, but was still in a wheelchair at the time the article was written. One VS patient (who had suffered a cerebral ischemic lesion) improved to the level of consciousness and currently responds to simple commands. Three VS patients died of respiratory infection, sepsis, or cerebrovascular insult (1 of each). The other 7 patients remained without substantial improvement of consciousness.

CONCLUSIONS Spontaneous recovery from MCS/VS to the level of consciousness with no or minimal need for assistance in everyday life is very rare. Therefore, if a patient in VS or MCS fulfills the selection criteria (presence of somatosensory evoked potentials from upper extremities, motor and brainstem auditory evoked potentials, with cerebral glucose metabolism affected not more than the level of hypometabolism, which is judged using PET), DBS could be a treatment option.

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KEY WORDS minimally conscious state; vegetative state; deep brain stimulation; centromedian-parafascicular nucleus; functional neurosurgery

Persistent vegetative state (PVS) was first described by Jennett and Plum in 1972 as wakefulness without awareness.[7] The Multi-Society Task Force defines the criteria for the diagnosis of vegetative state (VS) as: 1) no evidence of awareness of self or environment and inability to interact with others; 2) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; 3) no evidence of language comprehension or expression; 4) intermittent wakefulness manifested by the presence of sleep-wake cycles; 5) sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival

ABBREVIATIONS BAEP = brainstem auditory evoked potential; CM-pf = centromedian-parafascicular; DBS = deep brain stimulation; DR = Rappaport Disability Rating Scale; EEG = electroencephalography; MCS = minimally conscious state; MEP = motor evoked potential; PET = positron emission tomography; PVS = persistent VS; RAS = reticular activating system; SEP = somatosensory evoked potential; TBI = traumatic brain injury; VS = vegetative state.

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with medical and nursing care; 6) bowel and bladder incontinence; and 7) cranial-nerve reflexes (pupillary, oculocephalic, corneal, vestibulo-ocular, and gag) and spinal reflexes preserved to various extents. The task force also reported that recovery of consciousness from a posttraumatic PVS is unlikely after 12 months, while recovery from a nontraumatic PVS after 3 months is exceedingly rare.[1,2]

In 2002, Giacino et al.[5] proposed the concept of the minimally conscious state (MCS), which is characterized by inconsistent but clearly discernible behavioral evidence of consciousness and can be distinguished from coma or VS.

One of the first groups to try to raise the level of consciousness with chronic deep brain electrical stimulation was Hassler et al. They reported on the results of chronic electrical stimulation started 21 weeks after the initial trauma in a patient with apallic syndrome, using electrodes positioned in the left rostral part of the thalamus and right pallidum internum. Over a period of 19 days of stimulation, a strong arousal effect was noted, along with some other improvements, such as spontaneous movements; however, no substantial changes in the level of consciousness were achieved.[6]

McLardy et al.,[9] reporting a 1964 case study of a patient who was comatose after neurotrauma, explored a broad range of parameters of stimulation of the upper pontine reticular formation but reported no improvement in the level of consciousness. Sturm et al. (1979)[16] delivered chronic electric neurostimulation to 1 patient who remained with a disorder of consciousness 3 weeks after clipping a basilar tip aneurysm. Bilateral stimulation was first tried with 1 electrode in the left rostral thalamus and 1 in the rostral part of the lamella medialis thalami on the right side. The right-side electrode was removed because it had no effect. However, the effect of the left electrode, through which stimulation was delivered for a period of 7 weeks, consisted of a rise in the level of clinical responsiveness and the ability to respond to simple commands; even some verbal interactions were possible.

Cohadon and Richer[4] stimulated the centromedian parafascicular (CM-pf) nuclei unilaterally in 25 patients in VS after neurotrauma. In 12 of the patients, no changes in neurological status occurred, and all 12 remained in VS during 1–10 years of follow-up. In the other 13 patients, recovery of some degree of consciousness was obtained. The authors suggested that deep brain stimulation (DBS) seems likely to accelerate recovery and possibly improves the final level of performance. They also suggested a predictive value of the response to DBS according to recovery potential in patients with severe brain injury.

The most extensive studies of DBS for VS and MCS were published in several papers by Tsubokawa and Yamamoto and colleagues.[17–20] They described selection criteria and the results of DBS in 21 VS patients and 5 MCS patients. In the VS cohort, they targeted the mesencephalic reticular formation (nucleus cuneiformis) in 2 cases and the CM-pf complex in 19 cases, while the CM-pf complex was targeted in all 5 cases of MCS patients. Eight of the 21 VS patients recovered from VS and were able to communicate through some speech or other responses, but they continued to require assistance with their everyday life and remained bedridden with severe disability. Four of the 5 MCS patients emerged from the bedridden state. All 8 patients who recovered from VS showed desynchronization on continuous electroencephalography (EEG) frequency analysis. Wave V of the auditory brainstem response and N20 of the somatosensory evoked potential could be recorded, although with a prolonged latency, while the pain-related P250 was recorded with an amplitude greater than 7 μV.[18]

Schiff et al.[15] evaluated DBS in a single MCS patient following a 6 month double-blind alternating crossover study and reported positive results. Magrassi et al. reported beneficial effects on spasticity and myoclonus from bilateral thalamic stimulation in 3 patients with disorders of consciousness, although there was no evidence of conscious behavior.[8] In this paper we report the long-term results of DBS of the CM-pf nuclei in VS and MCS patients, focusing on clinical improvement with a follow-up period of at least 2 years.

Methods

In all cases in this series, we obtained informed consent from the responsible relatives and caretakers of the patient, after discussion and informing them of the experimental status of DBS of the CM-pf nuclei in VS and MCS patients, alongside with the possible complications and eventual benefits of the therapy. This study was approved by the ethics committee of the University Hospital Dubrava and the Croatian Ministry of Health.

Neurophysiological and Neuroradiological Evaluation

Patients in VS and MCS were selected for DBS based on electrophysiological evaluation with somatosensory evoked potentials (SEPs), motor evoked potentials (MEPs), brainstem auditory evoked potentials (BAEPs), and 12/24-hour EEG. SEPs were triggered by stimulation of median nerves at the wrist and posterior tibial nerves at the ankle with recording over the primary somatosensory cortex using subcutaneously placed corkscrew electrodes (CS electrode, Inomed GmbH). MEPs were induced by transcranial electrical stimulation (TES) with the montage C1 versus C2 according to a 10/20 EEG system. TES parameters consisted of 3–5 stimuli with individual stimulus duration 0.5 msec each (short train). These stimuli were spaced every 4 msec with a train repetition rate of 2 Hz and with an intensity of up to 200 mA. Trains were delivered through subcutaneously placed corkscrew electrodes, identical to those used for recording SEPs. Subdermal needle electrodes (Inomed GmbH), inserted into the abductor pollicis brevis and tibial anterior muscles, were used for the recording of MEPs. Far-field short-latency BAEPs were bilaterally recorded by unilateral stimulation of each ear. Click stimuli were delivered through the ear insert while noise to the contralateral ear was masked. Alternating clicks with an intensity of 100 dB and a stimulation rate of 11 Hz were used. Recordings were performed by means of corkscrew electrodes attached to the left or right ear lobe versus the frontopolar central electrode.

Two-channel EEG was recorded with C3′/CZ and

TABLE 1. Scoring of the Rappaport Coma/Near-Coma Scale

Level	Range (D)	Level of Awareness/Responsivity
0:	0.00–0.89:	No coma: consistently and readily responsive to at least 3 sensory stimulation tests plus consistent responsitivity to simple commands.
1:	0.90–2.00:	Near coma: consistently responsive to stimulation presented to two sensory modalities and/or inconsistently or partially responsive to simple commands.
2:	2.01–2.89:	Moderate coma: inconsistently responsive to stimulation presented to two or three sensory modalities but not responsive to simple commands. May vocalise (in absence of tracheostomy) with moans, groans and grunts but no recognisable words.
3:	2.90–3.49:	Marked coma: inconsistently responsive to stimulation presented to one sensory modality and not responsive to simple commands.
4:	3.50–4.00:	Extreme coma: no responsivity to any sensory stimulation.

From Rappaport M: The Disability Rating and Coma/Near-Coma scales in evaluating severe head injury. *Neuropsychol Rehabil 15*:442–453, 2005. Reprinted by permission of the publisher (Taylor & Francis Ltd., http://www.tandfonline.com).

C4′/CZ montages over a 12- or 24-hour period using corkscrew electrodes. The results of an automated EEG frequency spectral analysis were displayed as a compressed spectral array. The compressed spectral array of the EEG provided a clear display of the frequency spectrum of the EEG over time. Each patient underwent radiological imaging with positron emission tomography (PET) and MRI. PET is an imaging technique that detects gamma rays emitted from a radionuclide introduced into the patient's body via a biologically active molecule, e.g., fluorodeoxyglucose (FDG). Patients were slightly sedated with propofol to abolish myoclonic jerks before neurophysiological and neuroimaging tests (MRI).

Neurological Evaluation

Patients selected for DBS were evaluated by means of the Rappaport Disability Rating (DR) Scale and the Coma/Near-Coma (C/NC) Scale[13] before electrode implantation, then weekly during the first 3 months following implantation, and once a month thereafter. The DR scale rates patients with respect to 4 categories: arousability, awareness and responsivity (scores for eye opening, communication ability, and motor response), cognitive ability for self-care activities (scores for feeding, toileting, and grooming), dependence on others (scores for the level of functioning), and psychosocial adaptability (scores "employability''). The DR scores range between 0 and 30, with higher scores reflecting greater disability. If DR scores were greater than 21, the C/NC categories were defined. To determine the C/NC category, the patient is subjected to a variety of stimuli that define certain parameters (auditory, command responsivity, visual, threat, olfactory, tactile, pain, and vocalization). There are 11 stimuli that need to be executed and scored. These scores are then added together and the sum is divided by the total amount of stimuli used. This quotient is called the range or average CNC score. The C/NC scores are determined according to the range. C/NC categories include: no coma (Level 0), near coma (Level 1), moderate coma (Level 2), marked coma (Level 3), and extreme coma (Level 4) (Table 1).[13]

Selection Criteria for DBS Unit Implantation

Neurophysiological criteria were: recordable SEPs, MEPs, and BAEPs, even with pathological parameters (e.g., prolonged latencies or prolonged central conduction time). The entry criterion was SEP obtainability via stimulation of median nerves, even without SEPs elicited by tibial nerve stimulation. The entry criterion for EEG was the presence of periods of desynchronized EEG during 12/24 hours of monitoring processed EEG. The PET entry criterion was the presence of metabolism of radioactive glucose in the brain. The patients who were inconsistently or partially responsive to simple commands were classified as MCS patients (C/NC Level 1). All patients in VS were consistently not able to respond to any simple command (C/NC Level 2–4).

Surgical Targeting and Procedure

An electrode was implanted stereotactically into the CM-pf complex of the thalamic intralaminar nucleus, preferably in the left hemisphere (Fig. 1). In patients with posttraumatic lesions, however, the electrode was placed in the better-preserved hemisphere.

The surgery was performed under general anesthesia, and the target was determined according to the anterior commissure–posterior commissure line identified on T2-weighted MRI and CT. Contiguous T2-weighted 2-mm axial MR images were obtained the day before surgery (1.5-T Magnetom Avanto, Siemens AG). A Leksell Coordinate Frame G (Elekta AB) was mounted on the patient's head with the base ring aligned to Reid's baseline. A CT scan was acquired with 0.7-mm-thick slices after placement of the Leksell frame. The calculation of the target and trajectory was performed on a Medtronic StealthStation using FrameLink planning software (Medtronic). Coordinates from the Schaltenbrand-Wahren Atlas were used to approximate the target of the CM-pf complex. The target was 9 mm posterior of the midcommissural point, 1 mm below the intercommissural line, and 3.5 mm lateral to the ventricular wall. The entry point was approximately 3.5 cm from the midsagittal line and 1.5 cm anterior to the coronal suture. The trajectory was planned to avoid passing through ventricles and sulci. A bur hole was drilled with an 8-mm trepan and shaped to accommodate the StimLoc lead-anchoring device (Medtronic). Dynamic impedance monitoring with a radiofrequency probe, 1.5 mm in diameter (Elekta AB), was used to ensure that the trajectory did not penetrate the ventricle. The radiofrequency probe was withdrawn and the DBS lead (Model 3389, Medtronic) was immediately implanted down the

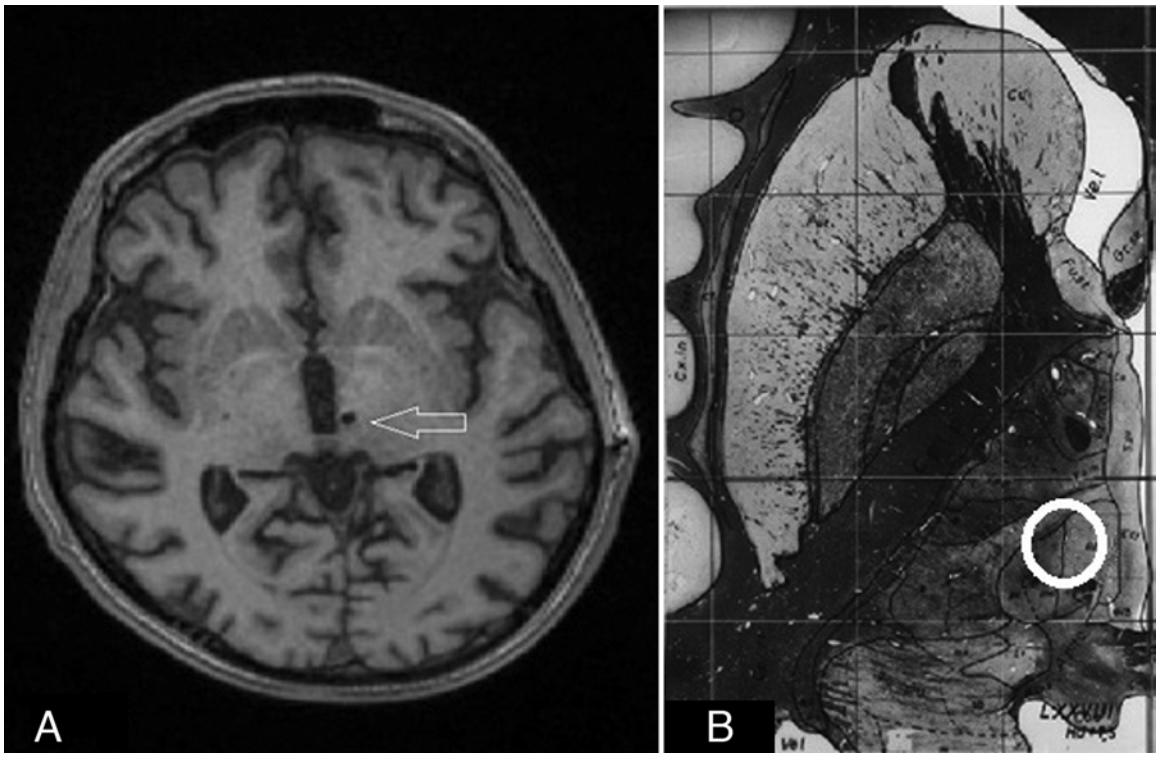

FIG. 1. Case 1. Electrode implanted in the left centromedian-parafascicular nucleus. **A:** Artifact of the electrode on axial T1-weighted MR image (*white arrow*). **B:** Position of the electrode on image from the Schaltenbrand-Wahren stereotactic atlas (*white circle*). From Schaltenbrand G, Wahren W: *Atlas for Stereotaxy of the Human Brain, ed 2.* Stuttgart: Georg Thieme Verlag, 1977, Fig. LXXV. Published with permission.

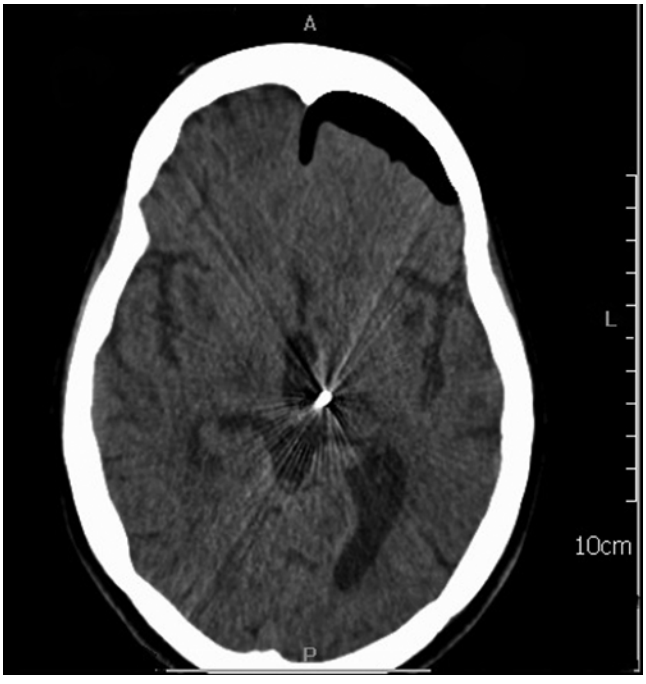

FIG. 2. Case 6. Immediate postoperative CT image revealing the position of the electrode and the presence of intracranial air with no visible sign of hemorrhage.

same trajectory. A postoperative stereotactic CT scan was obtained immediately after implantation of the lead to confirm the position of the electrode (Fig. 2).

The Leksell frame was removed, and an Activa SC pulse generator (Medtronic) was implanted in the subclavicular area. The day after surgery, T1-weighted MR images were acquired to ascertain the position of the electrode relative to the anterior-posterior commissure line and ventricle wall and to confirm the absence of postoperative intracranial hemorrhage (Fig. 3).

Monopolar stimulation was started on the 3rd postoperative day, using the contact eliciting the strongest arousal response (see Fig. 5) with minimal current, using 25-Hz frequency and 90-μsec pulse width. The voltage varied among the patients from 2.5 to 3.5 V. Stimulation was applied for a 30-minute period every 2 hours during the daytime.

Results

The neurophysiological criteria described above were fulfilled by 10 of 45 VS candidates and by all 4 MCS patients. Age, sex, etiology, and time to initiation of DBS are presented in Tables 2 and 3. In the VS group, the patients' age ranged from 16 to 59 years (average 35 years). Six of the 10 patients were male and 4 were female; 3 were in VS due to trauma and 7 were in VS following an anoxic lesion due to cardiac arrest. The length of time from the injury to initiation of DBS ranged from 2.5 to 21.5 months in this group. In the MCS group, the patients' age ranged from 16

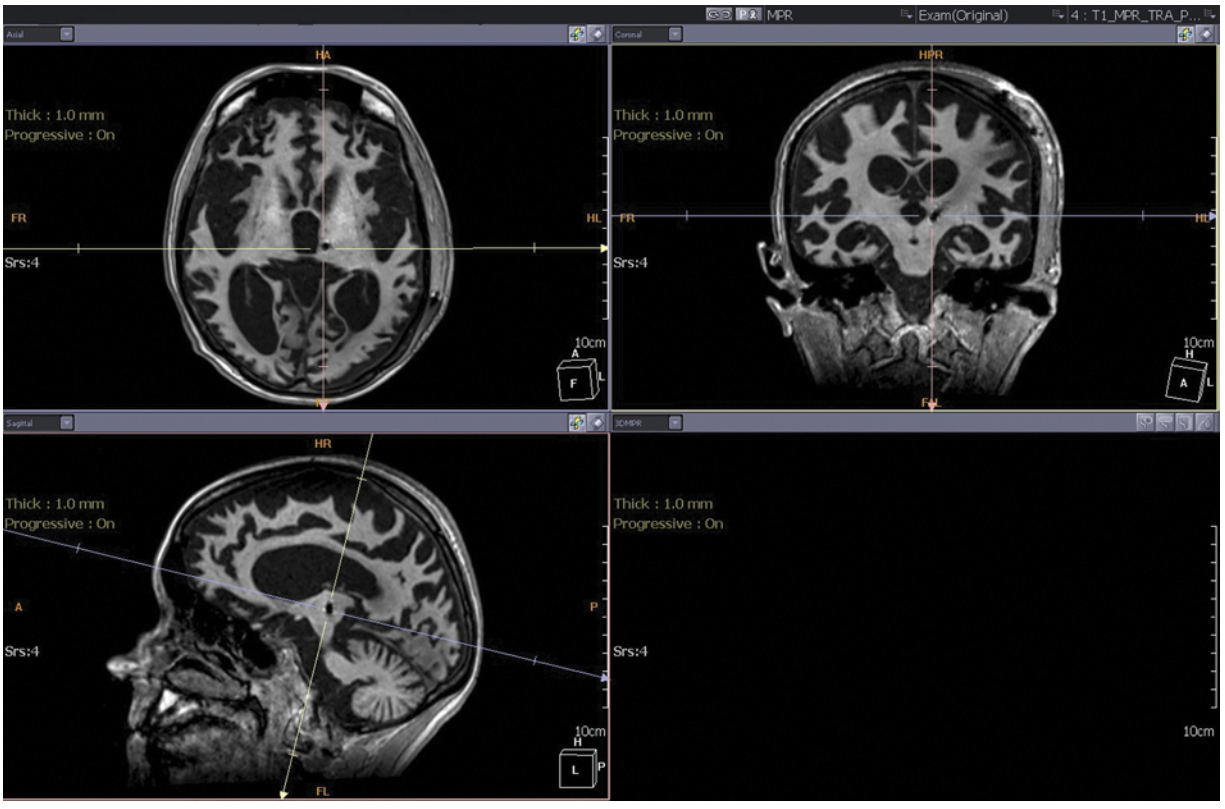

FIG. 3. Case 9. Postoperative T1-weighted MR images confirming the position of the electrode in the CM-pf complex. Figure is available in color online only.

to 28 years (average 20 years). The group included 3 male patients who had sustained cardiac arrest and 1 female patient who had been injured in a car accident (Table 2). The length of time from the injury to initiation of DBS ranged from 65 days to 11.5 years in this group.

MRI revealed the progression of ischemic encephalopathy with marked brain atrophy in all 14 patients (Fig. 4). In patients with marked posttraumatic lesions, the DBS lead was implanted in the more preserved hemisphere.

In each patient DBS provoked an arousal effect during stimulation (Fig. 5, Video 1).

VIDEO 1. Case 10. Video clip showing arousal reaction of an MCS patient after DBS was turned on. Copyright Darko Chudy. Published with permission. Click here to view.

This effect consisted of eye opening (if the patient's eyes were closed), with mydriasis and different facial expressions compared with before stimulation. Some of the patients turned their head in one direction and had elevation of their blood pressure along with heart rate elevation. A typical arousal response is presented in Fig. 5. For treatment, we used a stimulation frequency of 25 Hz exclusively. However, we also tested stimulation at 100 Hz, and this also elicited arousal. There were no side effects during programming. In all 3 patients who emerged from MCS and also in the 1 VS patient who regained responsiveness, the arousal effect gradually disappeared as their level of consciousness increased. In the patients whose condition did not improve, the arousal effect diminished slightly over several months of treatment.

The Rappaport C/NC scale values before DBS and at the end of follow-up for each patient are listed in Table 3. The MCS patients were classified according to their ability to respond to these specific commands: the patient in Case 1 inconsistently but clearly responded to a command to close his eyes (Video 2), the patient in Case 5 inconsistently responded with yes or no head nodding, and the patient in Case 10 responded to the command to raise her finger.

TABLE 2. Summary of demographic and clinical characteristics of patients in this study

Characteristic	VS (10 patients)	MCS (4 patients)
Age in yrs		
Mean	35	20
Range	16–59	16–28
Sex		
Male	6	3
Female	4	1
Etiology		
Traumatic	3	1
Anoxic	7	3
Time to DBS (range)*	2.5–21.5 mos	65 days–11.5 yrs

Values are numbers of patients unless otherwise indicated.
* Length of time between initial trauma or anoxic injury and DBS.

TABLE 3. Summary of demographic and clinical characteristics of 14 patients who underwent DBS

Case No.	Sex	Cause of Injury	Age at Injury (yrs)	Time to DBS (mos)*	Level of Awareness†		Duration of FU (mos)
					Before DBS	After DBS	
1	M	CA	17	2	2.0/1, MCS	0, aware	60
2	M	TBI	25	5	3.6/4, VS	3.4/3, VS	59
3	F	CA	49	6	3.6/4, VS	2.6/2, VS	58
4	M	CA	20	3	3.4/3, VS	3.0/3, VS	57
5	M	CA	23	2	1.8/1, MCS	0, aware	57
6	M	CA	59	2	3.8/4, VS	3.0/3, VS	56
7	M	CA	34	7	3.0/3, VS	Died	18
8	F	TBI	28	17	2.22/2, VS	2.1/2, VS	53
9	F	CA	39	7	3.8/4, VS	Died	4
10	F	TBI	15	11	1.6/1, MCS	0, aware	51
11	M	CA	17	137	1.0/1, MCS	1.0/1, MCS	50
12	M	TBI	43	21	3.2/3, VS	Died	33
13	M	CA	17	3	3.4/3, VS	2.2/2, VS	43
14	F	CA	16	4	2.6/2, VS	0, aware	38

CA = cardiac arrest; FU = follow up.
* Time from injury to initiation of DBS.
† Values represent range score/level on the Rappaport Coma/Near-Coma Scale.

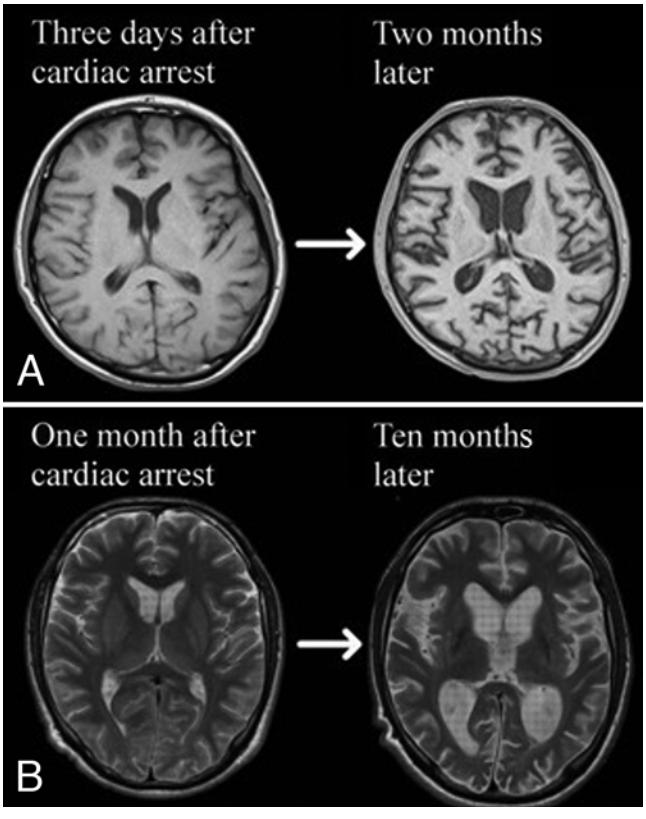

FIG. 4. MR images obtained in 2 patients with a similar MRI appearance. The upper pair of images (**A**) are from a patient in MCS (Case 1), who satisfied the entry criteria for the study and underwent DBS electrode implantation, resulting in a complete recovery of consciousness. The lower pair of images (**B**) are from a patient who did not satisfy entry criteria for the study. Note the brain atrophy with enlarged ventricles and pronounced sulci after 2 months (A, *right*) and 10 months (B, *right*) in coma compared with the MR images obtained 3 days and 1 month after cardiac arrest (*left* images in A and B).

VIDEO 2. Case 1. Video clip recorded preoperatively showing the patient in MCS. Note that he turns his head on call. Copyright Darko Chudy. Published with permission. Click here to view.

Three of 4 patients in MCS emerged to full awareness, with the ability to interact and communicate. Two of them are, as of this writing, able to live largely independently. One patient (Case 1), who began DBS 75 days after cardiac arrest suffered from dysarthria, dyscalculia, and dyslexia after regaining consciousness (Video 3); however, after a year of rehabilitation he recovered completely.

VIDEO 3. Case 1. Video clip recorded 3 months after DBS surgery showing the patient walking independently. Copyright Darko Chudy. Published with permission. Click here to view.

The other patient (Case 5), who began DBS 65 days after cardiac arrest, still experiences short-term memory impairment and emotional regression. Conventional diagnostic workup showed no evidence of structural heart disease in either of these young MCS patients. One of them (Case 1) had signs of early repolarization syndrome in his 12-channel electrocardiogram. The patient survived cardiac arrest and cardioverter-defibrillator implantation was performed for secondary prevention of sudden cardiac death. Cardiac electrophysiological diagnostic testing in the patient in Case 5 did not reveal any abnormality. The third patient (Case 10) did not begin DBS until 300 days after a traumatic brain injury (TBI) sustained in a car accident; she is still in a wheelchair, has severe left hemiparesis, and needs assistance in everyday life (Video 4).

VIDEO 4. Case 10. Video clip recorded 12 months after DBS surgery at a regular follow-up visit showing the patient following simple commands (changing view angle on command). Copyright Darko Chudy. Published with permission. Click here to view.

Long-term follow-up results for these MCS patients, who all became aware, are presented in Fig. 6.

One patient in VS (Case 14), in whom we started with DBS 4 months after cardiac arrest caused by electric shock, emerged to full awareness. This patient is still bed-

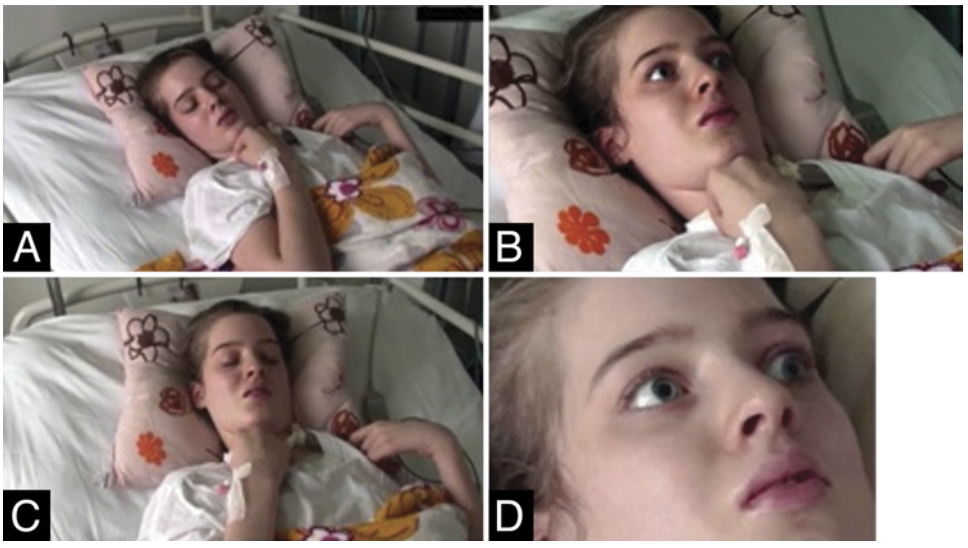

FIG. 5. Case 10. Arousal effect in VS patient during DBS of CM-pf nuclei. **A:** Stimulation OFF. **B:** Stimulation ON (during the ON phase of stimulation eyelids are widely open, pupils are dilated, and gaze is fixed). **C:** Stimulation OFF. **D:** Enlargement of patient's face from the image in panel B. (Images published with written permission of relative.)

ridden but obeys simple commands delivered by a physical therapist. The time frame of this patient's progression from injury and VS through MCS (after DBS) to full awareness is presented in Fig. 7.

Three of the VS patients died at different lengths of time after DBS implantation—one due to pneumonia after 4 months, one due to sepsis after 18 months, and one after cerebrovascular insult 33 months after implantation. There was no case of postoperative intracranial bleeding or postoperative infection, such as meningitis or wound infection. The absence of infectious complications was likely to be due in part to regular microbiology surveillance cultures, which are useful as a strategy for guidance of empirical therapy or its modification. After DBS implantation, if clinically indicated, surveillance cultures (urine samples, nasal and throat swabs, tracheal aspirates, skin swabs, and wound aspirates) were taken, and in case of infection, appropriate antibiotic therapy was tailored accordingly. Two VS patients and 1 MCS patient had seizures during DBS, which were controlled with antiepileptic drugs, allowing DBS to proceed. Three patients had anoxic myoclonic jerks before DBS, 2 of these patients were in MCS (Cases 1 and 5) and 1 was in VS (Case 14). They had been taking Rivotril (clonazepam) and Depakine (valproate) preoperatively, and in all 3 patients, the symptoms of myoclonus diminished and disappeared several days after the initiation of DBS of the CM-pf complex, and therefore antimyoclonic therapy was discontinued.

Discussion

We reported that DBS of the CM-pf nuclei in a group

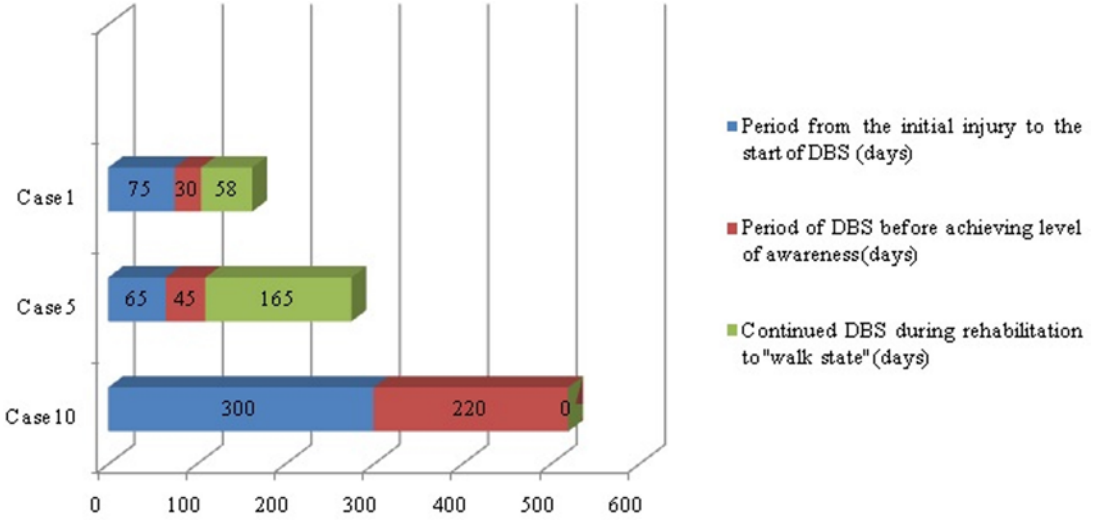

FIG. 6. Time course of recovery in MCS patients. Three of 4 patients in MCS recovered to C/NC Level 0 (aware, no coma). Two of these patients (Case 1 and Case 5) regained the ability to walk and talk, while the third patient (Case 10) improved to the point of being able to respond to simple commands. The x-axis shows time in days.

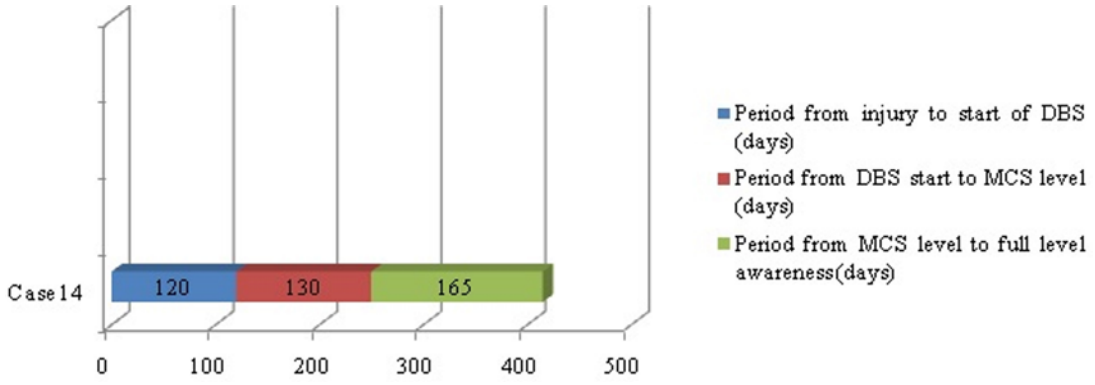

FIG. 7. Time course of recovery for the VS patient (Case 14) who gained the ability to respond to simple commands. The x-axis shows time in days.

of 14 patients in VS or MCS resulted in raising consciousness in 4 cases (29%). In 3 of these 4 cases, the patients were in VS or MCS due to ischemic encephalopathy. We are aware of the fact that it is not possible at this moment to completely rule out the possibility that some of our positive results may represent spontaneous improvements as opposed to a response to DBS treatment. However, the patients in Cases 1 and 5, who recovered the ability to walk and talk after DBS, improved rather quickly, over 3 months and 7 months, respectively, following the initiation of stimulation, which was initiated relatively early, approximately 2 months after the cardiac arrest, in both cases. Patients' level of responsiveness is crucial for physical and rehabilitative therapy, and an improvement of consciousness could substantially accelerate recovery. We acknowledge that beginning DBS this early limits our ability to clearly establish whether the recovery was spontaneous or due to DBS. However, the rate of recovery that we observed after DBS in this group of patients is significantly above the rate of spontaneous recovery previously reported.[1,2]

The CM-pf complex was used as a target for stimulation in patients in VS and MCS because a review of the literature revealed that it is the most used target with promising results in changing the state of patients' consciousness. The largest group of VS or MCS patients treated with DBS is a series of 21 VS patients reported on by Yamamoto et al.,[18] and in that series, 8 of the 21 patients recovered from VS to some degree of consciousness after DBS of the CM-pf nuclei. In that study, Yamamoto et al. also employed unilateral stimulation—mainly in the left hemisphere for right-handed patients, otherwise in the most preserved hemisphere.

Selection of the parameters for DBS in our study was derived from the experience of Yamamoto et al.[18] The arousal effect was induced in all patients, but it did not have any prognostic value for possible long-term effect in gaining consciousness other than its immediate dramatic effect, which we interpreted as a sign that the target was reached and entire stimulating system was in order. Stimulation of the triangle of Sano can elicit effects that mimic arousal,[3] but this region is quite distant from our target point. The arousal effect is not specific to the CM-pf nuclei. Moll et al.[11] reported a case of an arousal response induced in a patient with cervical dystonia who had DBS of the globus pallidus internus under general anesthesia.

The primary selection criteria for our patients were neurophysiological, although we also used PET, MRI, and clinical evaluation with the Rappaport Coma/Near-Coma Scale (C/NC). We also added MEPs to the set of neurophysiological tests. Of 45 VS patients considered for DBS surgery, 35 were excluded due to the absence of SEPs or MEPs in response to stimulation. We consider cortical SEPs to be the best neurophysiological markers for preservation of the functional integrity of the cerebral cortex.

We did not perform P300 neurophysiological testing, despite its prior use as a prognostic sign for recovery from MCS and VS. We contend that it would not have changed the results of our study, because in patients without cortical SEPs, P300 is not present. Therefore we did not overlook any potential candidate from the group of 35 patients in whom we did not proceed with implantation of DBS. Obviously, we are missing one or more stones in the mosaic of testing the functional integrity of the thalamocortical reticular activating system (RAS), a key element in maintaining consciousness. It appears, at least in some of the patients suffering from hypoxic encephalopathy, that an acute attack of cerebral ischemia may cause relatively little damage to the cerebral cortex, while seriously damaging the thalamocortical RAS. We speculate that such damage to the RAS may have been reversible in the patients we managed to "wake up" and irreversible in the patients who did not respond to treatment. Long-term EEG recordings can only indicate the relative preservation of RAS, but cannot resolve between reversible and irreversible damage. A histological study[14] in patients who died of hypoxic encephalopathy showed that the degree of severity of thalamic lesions was highly dependent on the duration of cerebral ischemia, which may explain the observed variation in recovery.

MR images obtained at early and late stages of MCS and VS patients, as shown in Fig. 4, illustrate the inability of MRI to distinguish between patients with different disorders of consciousness and the rapid course of brain atrophy in both conditions. This example may support early DBS in patients who satisfy neurophysiological criteria.

In some patients, DBS was started rather early after ischemic injury. In 2 MCS patients (Cases 1 and 5), DBS was started 2 months after cardiac arrest (ischemic brain lesions) and both of them recovered to awareness as well as the ability to walk, communicate, and live in-

dependently. One of the aforementioned patients (Case 1) reached this level of function after only 3 months of DBS combined with physical and speech therapy while another progressed to independence after seven months of rehabilitation. In another patient (Case 10) who was in MCS following traumatic brain injury, we started with DBS 11 months after injury and the patient recovered to the level of responsiveness. In contrast, the only MCS patient in this series without any improvement was the one in whom we started DBS 11 years after traumatic brain injury (Case 11).

We selected candidates for DBS from a pool of patients with disorders of consciousness in whom the initial injury had occurred from 65 days to 11 years previously. The Japanese groups reported success in improving the awareness of VS patients in whom they began DBS 4–8 months after injury. Schiff et al.[15] and Magrassi et al.[8] started DBS from 6 months to 6 years after injury, but without substantial improvement in patients' awareness. Definition of the clinical state of MCS and VS depends in part upon time elapsed subsequent to the precipitating injury. Six months after injury was the inclusion criterion for patients with a permanent disorder of consciousness in the report from Magrassi et al.,[8] while 1 year postinjury was the criterion used by Schiff et al.[15] The time since injury is important in the definition of permanent VS and MCS because the possibility of spontaneous recovery is much lower after 6 months or 1 year. Spontaneous recovery from VS associated with an ischemic lesion is extremely rare after 3 months postinjury and recovery of consciousness from VS is unlikely 6 months after the initial traumatic injury.[1,2] In our VS patient who gained awareness, we started with DBS 4 months after the ischemic event/nontraumatic injury.

Some authors[12] recommend that DBS should only be initiated after all forms of noninvasive therapy for consciousness disorders, such as transcranial magnetic stimulation, have been attempted. However, consistent evidence of the efficacy of these suggested modalities is still lacking. Consideration of DBS treatment should be driven by the possible risks and benefits, which should be foremost in the discussion with families and caretakers, who should be guided to realistic expectations to the extent possible. In a group of cases reported by Yamamoto et al., the success of improving the level of consciousness in VS patients was as high as 38% (8 of 21 treated patients).[18] Unfortunately, all 8 patients were still bedridden but could communicate to varying degrees with families or caretakers. The authors did not report postoperative intracranial bleeding or any other major complications.

With regard to the beneficial effect upon myoclonic jerks, our results are similar to those reported by Magrassi et al.[8] Following stimulation of the central thalamic area we observed diminishing and disappearing myoclonism a few days after beginning DBS of CM-pf nuclei.

A dilemma of candidate selection remains, as we still have no definitive neurophysiological or neuroradiological criteria that reliably predict who among VS or MCS patients may benefit from DBS. However, we do have neurophysiological markers for patients who are not candidates for DBS. New neuroradiological methods, such as MRI employing hyperpolarized isotopes, may reveal the metabolic status of neurons in certain relevant neuroanatomical structures in VS or MCS patients, which could lead to refined criteria regarding the indications for DBS treatment.[10]

Conclusions

We have reported on our attempt to aggressively approach the medically nontreatable conditions of VS and MC, and add to the growing body of literature on the use of DBS in this context. DBS of CM-pf nuclei in VS and MCS could be helpful not only in the treatment of spasms and myoclonic jerks but may also prove beneficial in addressing the underlying disorder of consciousness. Improving the level of awareness to responsiveness is crucial for physical therapy. Our results, combined with a review of previous literature, suggest that implementation of DBS in VS or MCS patients a long time after injury offers no possibility for the recovery of consciousness to the level of responsiveness.

We hope that this study can shed help to develop criteria for the selection of patients in those conditions. Our success rate in the selected group of patients is 29% (4 of 14 patients). We consider this a nonnegligible percentage of success, comparing favorably with studies of spontaneous recovery from ischemic cerebral lesions.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Chudy, Deletis. Acquisition of data: all authors. Analysis and interpretation of data: Chudy, Deletis, Almahariq, Marčinković, Paradžik. Drafting the article: Chudy, Deletis. Critically revising the article: Chudy, Deletis, Almahariq, Marčinković, Škrlin. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chudy. Administrative/technical/material support: Almahariq, Marčinković, Paradžik. Study supervision: Chudy, Deletis, Škrlin.

Supplemental Information

Videos

Video 1. https://vimeo.com/210779871.
Video 2. https://vimeo.com/210779575.
Video 3. https://vimeo.com/210779740.
Video 4. https://vimeo.com/210780034.

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