Original article

Deep brain stimulation therapy for vegetative state: indication and long-term follow-up results

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SUMMARY: *Twenty-one patients in a vegetative state, caused by various types of brain damage, were evaluated neurologically and electrophysiologically 3 months after the brain injury. These 21 patients were then treated using deep brain stimulation therapy, and followed up for over 10 years. The stimulation sites were the mesencephalic reticular formation (2 patients) and the centromedian/ parafascicularis nucleus complex (19 cases). Eight of the patients recovered from vegetative state, and became able to obey verbal commands, despite remaining bedridden. These 8 patients had shown desynchronization on continuous EEG frequency analysis. The Vth wave of the auditory brainstem response and N20 of somatosensory evoked potential was recordable, albeit with a prolonged latency, and pain-related P250 with an amplitude of over 7 mV had been registered. deep brain stimulation therapy may be useful for the recovery of patients from vegetative state, but candidates must be selected on the basis of electrophysiological criteria. Considering the finding that most of the patients who recovered from vegetative state remained in a bedridden state, a specific rehabilitation program combined with deep brain stimulation therapy is necessary. Patients in the minimally conscious state appear to be good candidates for deep brain stimulation therapy, since 4 of our 5 minimally conscious state patients recovered from their bedridden state.*

KEY WORDS: *Deep brain stimulation, Centromedian–parafascicular nucleus complex, Mesencephalic reticular formation, Minimally conscious state, Spinal cord stimulation, Vegetative state.*

INTRODUCTION

As a result of progress in modern intensive medical therapy, many patients who would once have died recover and resume their normal social activities. Although many lives are saved, the number of patients who survive for long periods in a prolonged coma is increasing. Among patients in prolonged coma, 30 to 40 percent fall into a persistent vegetative state[15,17]. The term persistent vegetative state was first proposed by Jennett and Plum[9], who, in 1972, described it as "*wakefulness without awareness*". The Multi-Society Task Force on PVS (1994)[12,13] summarized the medical aspects of PVS as follows: "the vegetative state is a clinical condition of complete unawareness of the self and the environment, accompanied by sleep-wake cycles, with either complete or partial preservation of hypothalamic and brainstem auto-

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LIST OF ACRONYMS AND ABBREVIATIONS: ABR = Auditory Brainstem Response; ABS = Deep Brain Stimulation; CM-pf = CentroMedian-parafascicular nucleus; $CMRO_2$ = Cerebral Metabolic Rate for Oxigen; CSA = Compressed Spectral Array; MCS = Minimally Conscious State; MRF = Mesencephalic Reticular Formation; SEP = Somatosensory Evoked Potential; OEF = Oxygen Extraction Fraction; PVS = Persistent Vegetative State; r-CBF = regional Cerebral Blood Flow; VS = Vegetative State.

nomic function. In addition, patients in a PVS show no evidence of sustained, reproducible, purposeful, or voluntary behavioural responses to visual, auditory, tactile, or noxious stimuli; show no evidence of language comprehension or expression; have bowel and bladder incontinence; and have variably preserved cranial-nerve and spinal reflexes."

We selected 21 patients on the basis of the above description of PVS; the patients had all remained in this state for more than 3 months after sustaining some type of brain damage. These 21 patients were evaluated neurologically and electrophysiologically 3 months after the brain injury, and were then treated using deep brain stimulation therapy (Figure 1). These patients have since been monitored for at least 10 years, assessing their long-term recovery of consciousness[10,20,23-26]. In addition, we compared the results of these DBS-treated PVS patients with those of minimally conscious state patients, also given DBS therapy[23,25].

□ PATIENTS AND METHODS

■ **Patients in vegetative state treated by DBS.** We use the term vegetative state to refer to PVS, because patients in such a state do not remain in a comatose state permanently. All of the 21 patients had been in a condition that satisfied the Multi-Society Task Force on PVS (1994) criteria for a diagnosis of VS for at least 3 months before undergoing DBS therapy, and all were followed up for more than 10 years after the treatment. Their ages ranged from 19 to 75 years old, and the causes of the initial coma were head injury (9 patients), cerebrovascular accident (9 patients), and anoxia (3 patients).

■ **Electrophysiological evaluation of VS.** Three months after the onset of the comatose state, neurological examination and neurophysiological testing were carried out. Neurophysiological testing included assessments of the ABR, SEP, pain-related P250[10], and continuous EEG frequency analysis, expressed as a CSA[21,23]. EEG recording was carried out at the bedside with a monopolar lead, and electrodes were placed in the parietal area and earlobe on both sides. EEG recording was displayed as a CSA for EEG frequency analysis, employing a fast Fourier transform. The CSA was classified into three types, similar to those used in the report by Bricolo[2], as follows:

1. *slow monotonous spectrograms*, whose main feature is the presence of pronounced peaks in the low-frequency band, recurring monotonously in separate samples,
2. *changeable spectrogram*s, whose spectra are characterized by constant and predominant activities at low frequencies associated with variously pronounced and organized peaks at alpha or higher frequencies, and
3. *borderline spectrograms*, whose main feature is that most of the power is centred in the alpha-frequency band, and whose peaks show an extremely regular and stable frequency (Figure 2).

We further classified the changeable spectrograms into three types, based on their distinct patterns, as follows.

(1) *No desynchronization pattern*: changes in peak frequency are present only at alpha and lower frequencies, not at higher frequencies.
(2) *Slight desynchronization pattern*: desynchronization (a change to low amplitude and high frequency) is present, but does not appear frequently; the duration is short, being under 10% of the time course, and the power of the higher frequency is low.
(3) *Desynchronization pattern*: desynchronization appears frequently, and the increase in high-frequency power at desynchronization is obvious (Figure 3).

The ABR was recorded by placing needle electrodes on the vertex (Cz), earlobes, and forehead (ground). The band pass was set from 10 Hz to 3 KHz. Earphones were used to administer 90-dB HL binaural click stimuli at a rate of 10/s. Each trial consisted of 2048 responses. SEP was recorded from a needle electrode placed over the primary cortical somatosensory regions on the head, with the reference electrode placed on the earlobe. The band pass was set from 0.5 Hz to 3 KHz. Pain-related P250 was recorded from the vertex in response to a train of electrical shocks applied at random intervals to the

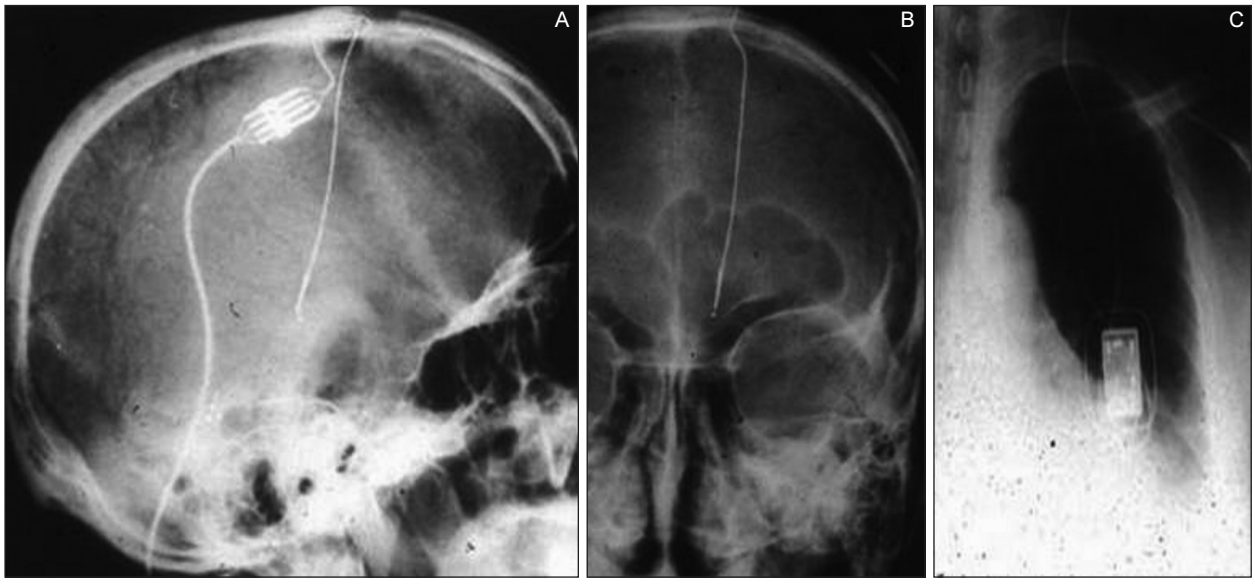

Figure 1. Deep brain stimulation for treatment of a vegetative state patient. The stimulating electrode was implanted for CM-pf stimulation. DBS electrode (A and B) and implantable pulse generator (C).

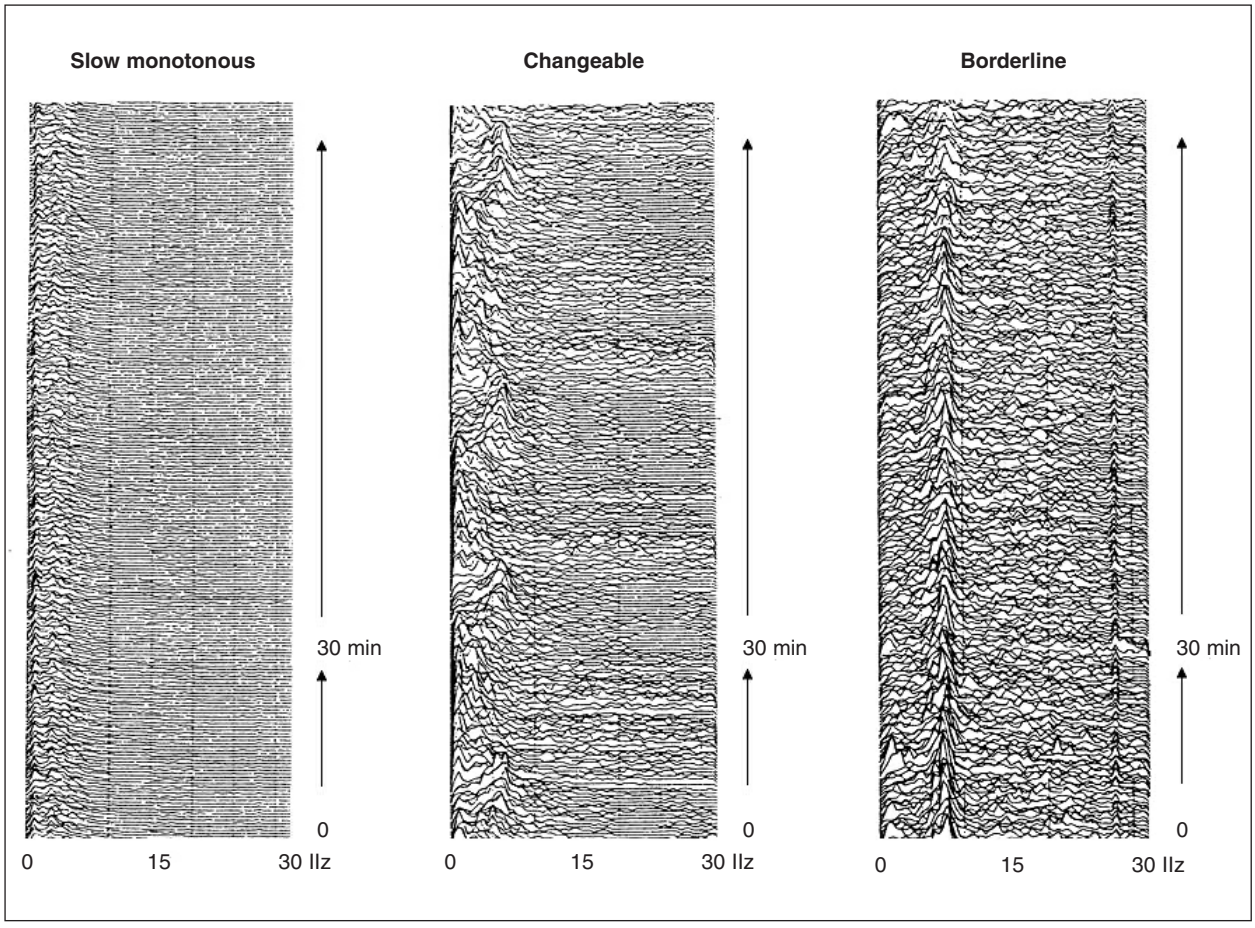

Figure 2. Three types of compressed spectral array of continuous EEG frequency analysis in prolonged coma patients.

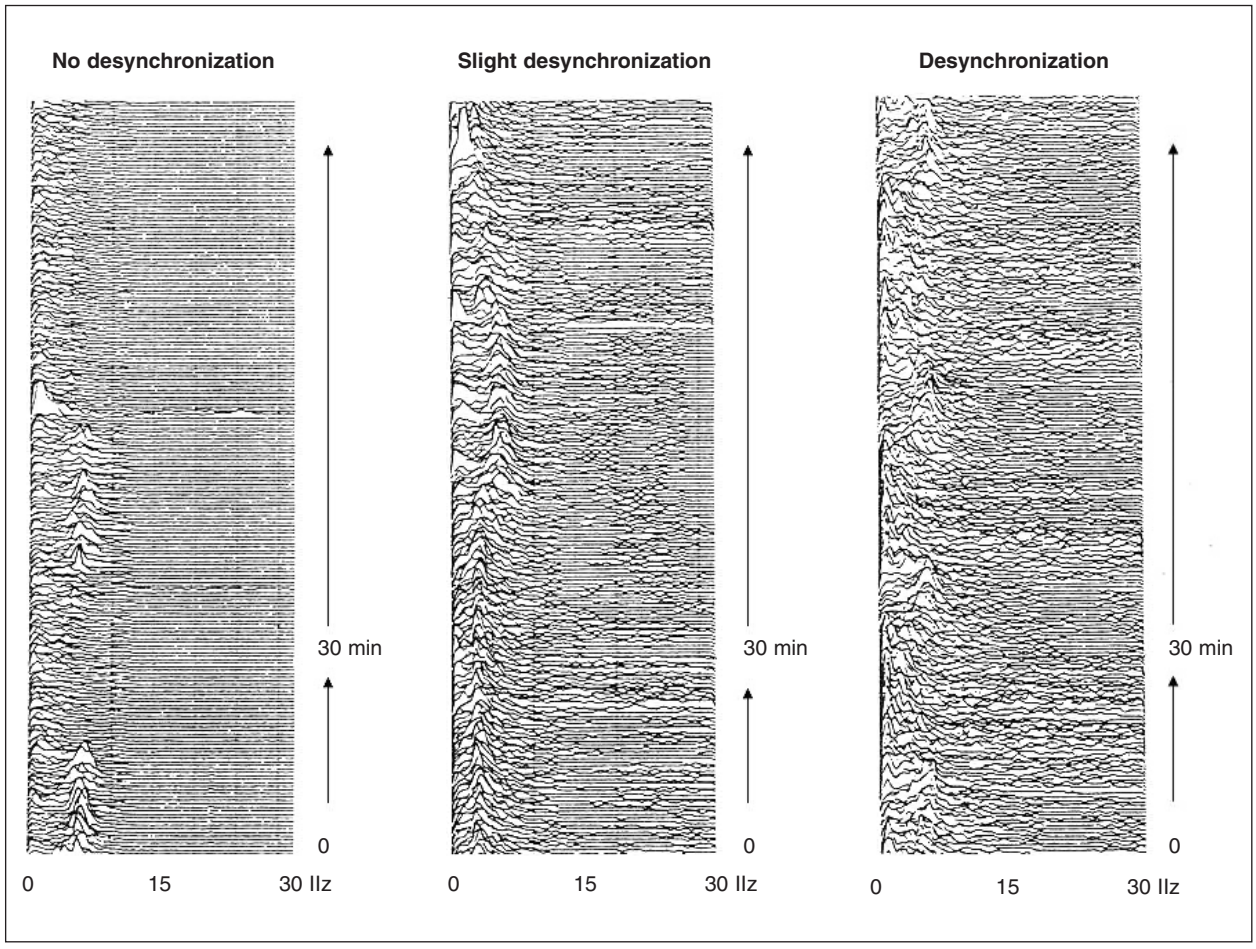

Figure 3. Changeable spectrograms were classified into: no desynchronization pattern, slight desynchronization pattern, and desynchronization pattern.

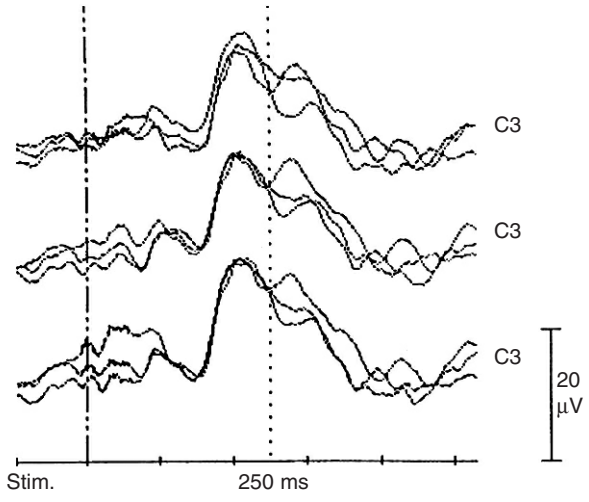

Figure 4. Pain-related P250 recording

finger pad. For painful electrical skin stimuli, constant current pulses of 0.5 ms duration were applied at a repetition rate of 500 Hz for 50 ms. The intensity of the stimulus was adjusted to a level that produced a flexion withdrawal reflex. Recording electrodes were referred to the earlobe and placed on the vertex and hand region of the somatosensory cortex. Grounding was to the other earlobe or the wrist. Signals were amplified with a band pass from 0.1 to 6000 Hz, and were averaged over 16 sweeps with a signal processor (Figure 4).

■ **DBS TREATMENT IN VS.** Chronic DBS was applied using a chronically implanted flexible wire electrode, inserted by stereotactic surgery under local anaesthesia. The mesencephalic reticular formation (2 patients) and the centromedian/parafascicularis nucleus complex (19 patients) were selected as target points for chronic DBS. Stimulation was applied every 2 to 3

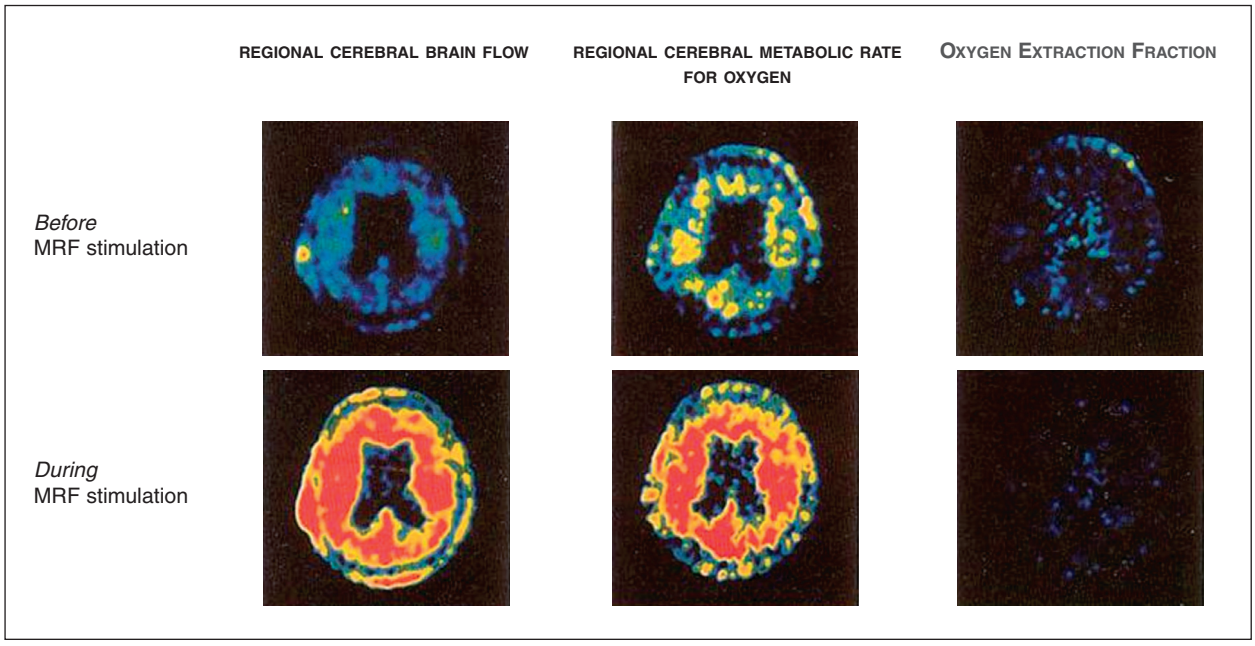

Figure 5. Alterations of r-CBF, regional $CMRO_2$, and OEF before and during stimulation of mesencephalic reticular formation in vegetative state patient (*modified from Tsubokawa T et al., Brain Inj 1990; 4 (4): 329-337*).

hours during the daytime, and was continued for 30 min each session. The frequency of stimulation was mainly fixed at 25 Hz, and the intensity of stimulation was regulated according to the response of each patient, being slightly higher than the threshold for inducing an arousal response.

When therapy was begun, we employed a chronically implanted flexible electrode (3380, Medtronic Inc., Minneapolis, Minnesota) and a transmitter-receiver system (3470 and 3425, Medtronic Inc., Minneapolis, Minnesota) to administer chronic DBS. After that, we used more comfortable electrodes (model 3387; Medtronic Inc., Minneapolis, Minnesota) and an implantable pulse generator (7426, Medtronic Inc., Minneapolis, Minnesota).

The target point in the MRF was the nucleus cuneiformis, which is located in the dorsal part of the nucleus ruber and the ventral part of the deep layer of the superior colliculus. The CM-pf complex was selected as the stimulation point in the non-specific thalamic nucleus.

During and after stimulation, the r-CBF, cerebral oxidative energy utilization ($CMRO_2$), and OEF were assessed by positron emission tomography.

We followed up the 21 patients for over 10 years, assessing both their consciousness and functional recovery.

□ RESULTS

❒ Stimulation-induced phenomena

The features of the stimulation at the given targets were such that the patients presented strong arousal responses that were observed immediately stimulation was begun. The patients opened their eyes; their pupils were dilated; the mouth sometimes opened widely, producing meaningless vocalizations; and a slight increase in systemic blood pressure was observed during the stimulation. Some patients also displayed slight movements of the extremities. The same phenomena were induced, irrespective of whether the MRF or the CM-pf complex was stimulated. On the basis of these findings, we mainly applied CM-pf complex stimulation, due to the safety issues linked electrode implantation at the other site.

During mesencephalic stimulation, both r-CBF and r-$CMRO_2$ increased markedly, but no change in OEF was observed (Figure 5).

❒ Neurological follow-up and outcome scale for DBS therapy in VS

We devised an itemized neurological follow-up scale for DBS therapy. This scale involves scoring 10 items

Score	Neurobehaviour
1	Alive with spontaneous respiration
2	Withdrawal response to pain
3	Spontaneous eye opening and closing
4	Spontaneous movement of extremities
5	Pursuit by eye movement
6	Emotional expression
7	Oral intake
8	Producing meaningful sound
9	Obeying orders
10	Verbal response

Table 1. Neurological follow-up scores of VS in patients with DBS therapy (*from Nihon University*).

(Table 1), and the number of positive items is taken as the follow-up outcome score, which therefore ranges from 0 to 10 points. Follow-up scores over 8 points indicate recovery from VS.

❒ Long-term effect of DBS therapy in VS

Eight of the 21 patients emerged from their VS, and were able to communicate with some speech or other responses, but still required some assistance with their everyday, bedridden life. Even after long-term rehabilitation, they all remained confined to bed, with the exception of 1 patient. The remaining 13 patients were unable to communicate at all, and failed to recover from VS (Figure 6). Based on the changes we observed in DBS follow-up score, it is necessary to continue the stimulation for at least 6 to 12 months, in order to be able to assess the efficacy of DBS therapy in terms of recovery.

In the 8 patients who recovered from VS following DBS therapy, the Vth wave of the ABR and N20 of SEP had been recorded, albeit with a prolonged latency; continuous EEG frequency analysis had revealed a desynchronization or slight desynchronization pattern; and pain-related P250 with amplitude of over 7 mV had been recorded.

These electrophysiological findings in patients in whom the therapy was effective provide useful information regarding the selection of candidates for deep brain stimulation.

❒ Comparison with results of DBS therapy in MCS patients

MCS is characterized by inconsistent but clearly discernible behavioural evidence of consciousness, and can be distinguished from coma and VS by the presence of specific behavioural features not found in either of these conditions. MCS is often transient, but may exist as a permanent outcome[6].

CM-pf complex stimulation was applied in 5 patients in MCS. All of these 5 patients in MCS had exhibited inconsistent behavioural evidence of consciousness before DBS therapy, and we hoped to determine whether they would recover from their bedridden state. Four of the five patients did so after DBS therapy, and were able to enjoy life in their own homes. The remaining 1 patient remained confined to bed. These findings indicate that MCS patients are more suitable candidates for DBS therapy with respect to VS[18,23].

□ DISCUSSION

In 1949, on the basis of their results on lesioning and local stimulation, Moruzzi and Magoun[14] proposed the concept of the ascending reticular activating system. Later anatomical studies revealed that widespread projection systems originating in the brainstem pass through these areas, and innervate wide areas of the cerebral cortex, giving them an important role in this activating system[1,11,22]. These findings are quite reasonable, because we can elicit a very strong arousal response by stimulating these areas, even in humans[7,20].

Temporary DBS therapy for the treatment of long-term comatose-state patients was first reported by Hassler et al. in 1969[7], and Strum et al.[19] in 1979. Hassler et al. stimulated the anterior thalamic nucleus, and observed a very strong arousal response. However, they were only able to continue stimulation for 19 days, and no signs of awareness were observed. More recently, however, chronic implantation systems for DBS have become available for clinical use, prompting Tsubokawa et al. (1990)[20] and Cohadon and Richer (1993)[3] to try DBS in VS.

DBS applied to the mesencephalic reticular formation or CM-pf complex can exert a strong arousal response, and elicit marked increases in r-CBF[20]. In VS, cerebrocortical functions are more disturbed than brainstem functions, and the relationship between the

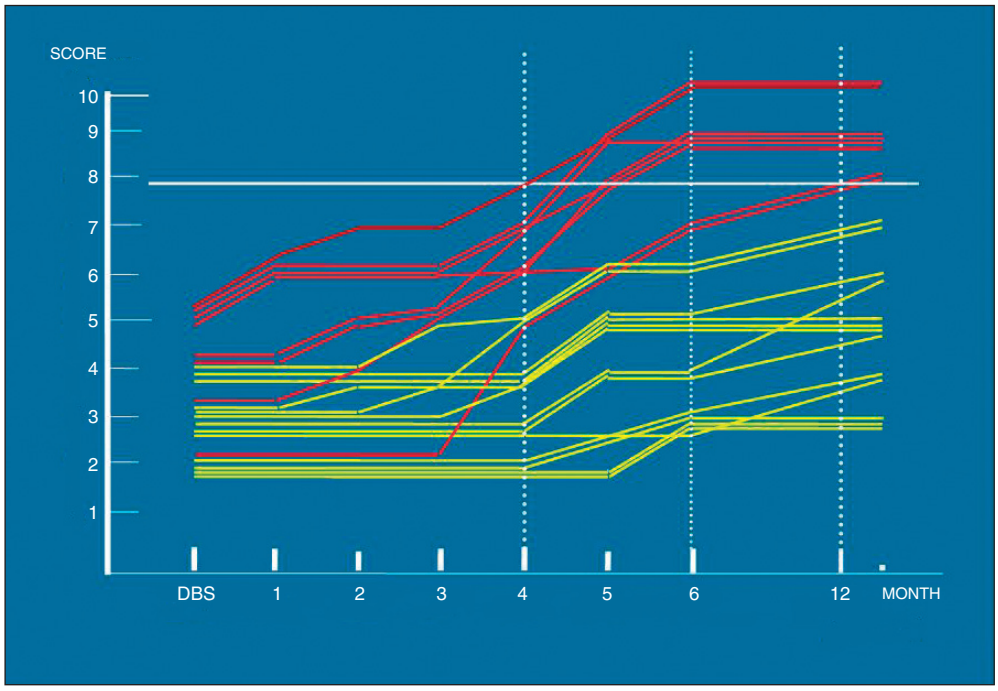

Figure 6. Changes in neurological follow-up score after the start of DBS therapy. *Red line* indicates patients recovering from VS, and yellow line indicates patients who remained in VS.

brainstem and cerebral cortex is important for maintaining consciousness.

We therefore predominantly stimulated the CM-pf complex during DBS therapy, as low-frequency electrical stimulation of the CM-pf complex can induce incremental recruiting and augment responses in EEG, and high-frequency stimulation provokes EEG desynchronization[4,5,8,16].

Reports of major series on recovery from VS have indicated that recovery of consciousness from post-traumatic VS is unlikely after 12 months, and recovery from non-traumatic VS after 3 months is exceedingly rare[18,19]. Our 8 patients who emerged from VS included 6 patients with cerebrovascular injury and 2 patients with traumatic injury. We emphasize here that chronic DBS therapy may be useful for the recovery of patients from VS, but candidate patients must be selected on the basis of electrophysiological criteria[21,23]. The above 8 patients remained bedridden, even after recovering from VS, and only one of these recovered from the bedridden state later on. In contrast, most of our MCS patients were no longer confined to bed after DBS therapy. Clinical applications of DBS therapy for MCS are thus more promising when considering the physically disabled state of patients who are recovering from VS. Considering the physical difficulties experienced after recovery from VS, DBS therapy should be used in conjunction with specific neurorehabilitation strategies.

REFERENCES

1. Aghajanian GK, Vandermaelen CP. Intracellular identification of central noradrenergic and serotonergic neurons by a new double labeling procedure. J Neurosci 1982; 2 (12): 1786-1792.
2. Bricolo A, Turazzi S, Faccioli F, Odorizzi F, Sciaretta G, Erculiani P. Clinical application of compressed spectral array in long-term EEG monitoring of comatose patients. Electroencephalogr Clin Neurophysiol 1978; 45 (2): 211-225.
3. Chohadon F, Richer E. Stimulation cerebrale profonde chez des patients etat vegetatif post traumatique. Neurochirurgia 1993; 39: 281-292.
4. Dempsey EWA, Morison RS. A study of thalamocortical relation.Am J Physiol 1942; 135: 291-292.
5. Dieckmann G. Cortical synchronized and desynchronized responses evoked by stimulation of the putamen and pallidum in cats. J Neurol Sci 1968; 7 (2): 385-391.
6. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, Zasler ND. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002; 58 (3): 349-353.
7. Hassler R, Ore GD, Dieckmann G, Bricolo A, Dolce G. Behavioural and EEG arousal induced by stimulation of

unspecific projection systems in a patient with post-traumatic apallic syndrome. Electroencephalogr Clin Neurophysiol 1969; 27 (3): 306-310.

8. Jasper HH, Naquet R, King EV. Thalamocortical recruiting responses in sensory receiving areas in the cat. Electroencephalogr Clin Neurophysiol 1955; 7 (1): 99-114.
9. Jennett B, Plum F. Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet. 1972; 1 (7753): 734-737.
10. Katayama Y, Tsubokawa T, Harano S, Tsukiyama T. Dissociation of subjective pain report and pain-related late positive components of cerebral evoked potentials in subjects with brain lesions. Brain Res Bull 1985; 14 (5): 423-426.
10. Katayama Y, Tsubokawa T, Yamamoto T, Hirayama T, Miyazaki S, Koyama S. Characterization and modification of brain activity with deep brain stimulation in patients in a persistent vegetative state: pain-related late positive component of cerebral evoked potential. Pacing Clin Electrophysiol. 1991; 14 (1): 116-121.
11. Kimura H, Maeda T. Aminergic and cholinergic systems in the dorsolateral pontine tegmentum. Brain Res Bull 1982; 9 (1-6): 493-499.
12. Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). N Engl J Med 1994; 330 (21): 1499-1508.
13. Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (2). N Engl J Med. 1994; 330 (22): 1572-1579.
14. Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1949; 1 (4): 455-473.
15. Pazzaglia P, Frank G, Frank F, Gaist G. Clinical course and prognosis of acute post-traumatic coma. J Neurol Neurosurg Psychiatry 1975; 38 (2): 149-154.
16. Sasaki K, Staunton HP, Dieckmann G. Characteristic features of augmenting and recruiting responses in the cerebral cortex. Exp Neurol 1970; 26(2): 369-392.
17. Sazbon L, Groswasser Z. Outcome in 134 patients with prolonged posttraumatic unawareness. Part 1: Parameters determining late recovery of consciousness. J Neurosurg 1990; 72 (1): 75-80.
18. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, Biondi T, O'Connor J, Kobylarz EJ, Farris S, Machado A, McCagg C, Plum F, Fins JJ, Rezai AR. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 2007; 448 (7153): 600-603.
19. Sturm V, Kühner A, Schmitt HP, Assmus H, Stock G. Chronic electrical stimulation of the thalamic unspecific activating system in a patient with coma due to midbrain and upper brain stem infarction. Acta Neurochir 1979; 47 (3-4): 235-244.
20. Tsubokawa T1, Yamamoto T, Katayama Y. Prediction of outcome of prolonged coma caused by brain damage. Brain Inj 1990; 4 (4): 329-337.
21. Tsubokawa T, Yamamoto T, Katayama Y. Prediction of the outcome of prolonged coma caused by brain damage. Brain Injury 1990; 4 (4): 329-337.
22. Vincent SR, Satoh K, Armstrong DM, Panula P, Vale W, Fibiger HC. Neuropeptides and NADPH-diaphorase activity in the ascending cholinergic reticular system of the rat. Neuroscience 1986; 17 (1): 167-182.
23. Yamamoto T1, Katayama Y. Deep brain stimulation therapy for the vegetative state. Neuropsychol Rehabil 2005; 15 (3-4): 406-413.
24. Yamamoto T, Katayama Y, Kobayashi K, Kasai M, Oshima H, Fukaya C. DBS therapy for a persistent vegetative state: ten years follow-up results. Acta Neurochir 2003 (Suppl);87: 15-18.
25. Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C, Katayama Y. DBS therapy for the vegetative state and minimally conscious state. Acta Neurochir 2005 (Suppl); 93: 101-104.
26. Yamamoto T, Katayama Y, Oshima H, Fukaya C, Kawamata T, Tsubokawa T. Deep brain stimulation therapy for a persistent vegetative state. Acta Neurochir 2002 (Suppl); 79: 79-82.