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Deep brain stimulation therapy for the vegetative state

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Twenty-one cases of a vegetative state (VS) caused by various kinds of brain damage were evaluated neurologically and electrophysiologically three months after brain injury. These cases were treated by deep brain stimulation (DBS) therapy, and followed up for over 10 years. The mesencephalic reticular formation was selected as a target in two cases, and the thalamic centre median-parafascicular (CM-pf) complex was selected as a target in the other 19 cases. Eight of the 21 patients emerged from the VS, and became able to obey verbal commands. However, they remained in a bedridden state except for one case. DBS therapy may be useful for allowing patients to emerge from a VS, if the candidates are selected according to appropriate neurophysiological criteria. A special neurorehabilitation system may be necessary for emergence from the bedridden state in the treatment of VS patients. Further, DBS therapy is expected to provide a useful method in minimally conscious state (MCS) patients to achieve consistent discernible behavioural evidence of consciousness, and emergence from the bedridden state.

INTRODUCTION

As a result of progress in emergency treatment, many patients who would have died previously now recover. Although many lives are saved, the number of patients in a vegetative state (VS) is increasing. The Multi-Society Task Force on PVS (1994a, 1994b) summarised the medical

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aspects of the VS. They provided a statement that the VS 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 autonomic function. In addition, patients in the VS 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. On the other hand, the definition and diagnostic criteria of the minimally conscious state (MCS) were reported in 2002 (Giacino et al., 2002). The MCS is characterised by inconsistent but clearly discernible behavioural evidence of consciousness and can be distinguished from coma and the VS by documenting the presence of specific behavioural features that are not found in either of these latter conditions. Retrospectively, our cases were classified as VS and MCS according to the above statements.

However, there are various grades of severity and various stages leading to various outcomes, even if the patient displays neurological signs identical to the VS (Katayama et al., 1991; Tsubokawa et al., 1990a; Tsubokawa, Yamamoto, & Katayama, 1990b; Yamamoto et al., 2001, 2003). We evaluated patients in the VS by an electrophysiological approach, and compared the results of the examination with the long-term prognosis. As a result, we found that, even if the symptoms are similar from a neurological point of view, the degree of brain injury varies to a considerable degree. Also, there will be a considerable number of patients who may not be able to recover spontaneously, but who can be saved from the VS by means of appropriate treatment (Katayama et al., 1991; Tsubokawa et al., 1990a, 1990b; Yamamoto et al., 2001, 2003). We report the long-term follow-up results of deep brain stimulation (DBS) therapy in comparison with the findings of electrophysiological evaluations in VS patients. In addition, the long-term effects of DBS therapy for the MCS are assessed comparatively.

METHODS

Materials

Retrospectively, our cases were classified as VS (21 cases) and MCS (5 cases) according to the above statements on the VS and MCS. These cases were evaluated neurologically and electrophysiologically at 3 months after brain injury. They received DBS therapy mainly between 3 and 6 months after brain injury, and only one VS case received it at 8 months after brain injury. We followed up these cases for a period of over 10 years and examined their long-term functional recovery. The ages of the VS patients ranged from 19 to 75 years (mean = 44.0), and the cause of the initial coma were head injury (9 cases),

cerebrovascular accident (9 cases), and anoxia (3 cases). The ages of the MCS patients ranged from 18 to 47 years (mean = 33.5), and the cause of the initial coma were head injury (3 cases) and cerebrovascular accident (2 cases).

Electrophysiological evaluations

The electrophysiological evaluations included assessments of the auditory brainstem response (ABR), somatosensory evoked potential (SEP), pain-related P250 and continuous electro-encephalogram (EEG) frequency analysis (Katayama et al., 1991; Tsubokawa et al., 1990b). The EEG was monitored continuously for at least 48 hours at the bedside, and also displayed as a compressed spectral array. We classified the continuous EEG frequency analysis into three types: (1) no desynchronisation pattern: changes of peak frequency were present only in the alpha and lower frequencies, and not in the higher frequencies; (2) slight desynchronisation pattern: desynchronisation was present but did not appear frequently; the duration was short, being under 10% of the time course, and the power of the high frequency was low; and (3) desynchronisation pattern: desynchronisation (a change to low amplitude and high frequency) appeared frequently, and the increase in the high frequency power was obvious at desynchronisation. The ABR recordings were classified into three patterns: (1) no response; (2) prolonged latency of the Vth wave; and (3) normal recordings. Prolonged latency of the Vth wave meant that the I–V wave latency was over two standard deviations longer than in normal cases. The SEP recordings, on the well-preserved side in cases where laterality was present, were classified into three patterns: (1) no N20; (2) prolonged N20; and (3) normal N20. Prolonged latency of N20 meant that the Erb-N20 latency was over two standard deviations longer than in normal cases recorded at our hospital. The pain-related P250 recordings were classified into three patterns: (1) no P250; (2) P250 recorded with under 7 μV; and (3) P250 recorded with over 7 μV.

Deep brain stimulation therapy

Chronic DBS was applied using a chronically implanted flexible wire electrode inserted by stereotactic surgery under local anaesthesia. As target points for the VS patients, the mesencephalic reticular formation (2 cases) and the CM-pf complex (19 cases) were selected, while the CM-pf complex (5 cases) was selected for the MCS patients. The features of the stimulation at the given targets were such that the patients presented strong arousal responses which were observed immediately at the start of stimulation. The patients opened their eyes with dilated pupils, the mouth sometimes also opened widely with meaningless vocalisations, and a slight increase in systemic blood pressure was observed during the

stimulation. Moreover, some cases revealed slight movements of the extremities, and the EEG showed desynchronisation during the DBS stimulation. Stimulation was given every 2–3 hours during the daytime, and was continued for 30 min at one session. The frequency of the stimulation was mostly fixed at 25 Hz, and the intensity was decided according to the responses of each individual patient, being at slightly higher than the threshold for inducing an arousal response. To apply the chronic DBS, we employed a chronically implanted flexible electrode (3380, Medtronic Co.) and a transmitter-receiver system (3470 and 3425, Medtronic Co.). The target point in the mesencephalic reticular formation was the nucleus cuneiformis, which is located in the dorsal part of the nucleus ruber and ventral part of the deep layer of the superior colliculus. The CM-pf complex (P, 7–9; L, 5–6; H, 0–1) was selected as the stimulating point in the non-specific thalamic nucleus (see Figure 1).

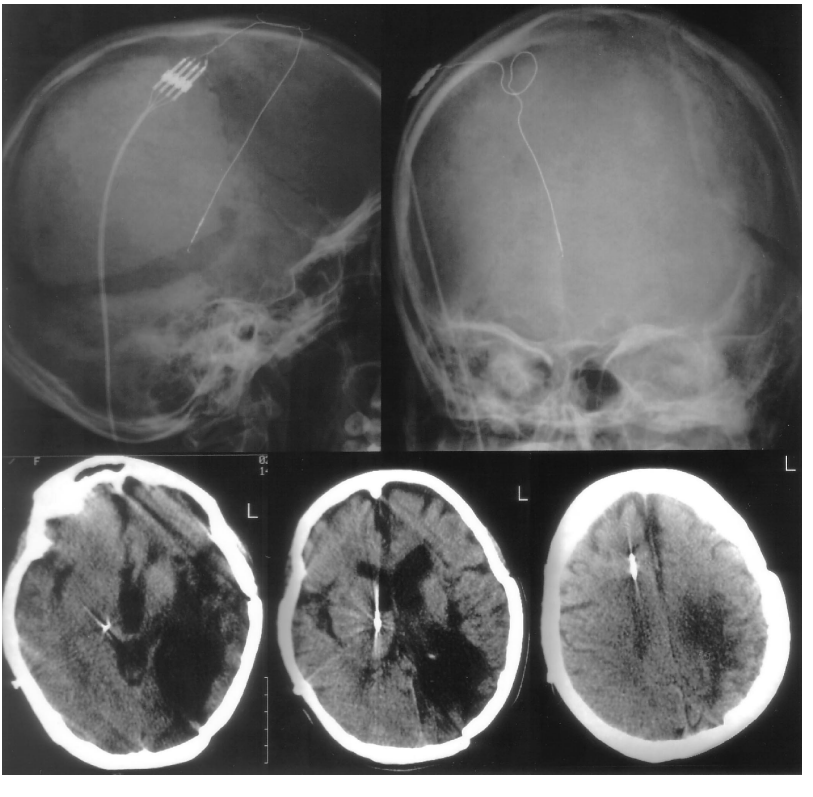

Figure 1. CM-pf complex stimulation therapy for VS. The skull X-P (upper) and axial CT scans (lower) indicate the location of the DBS electrode

RESULTS

Effects of DBS for the VS

The main feature of the present stimulation therapy was that the patients presented strong arousal responses as mentioned earlier, which were observed immediately at the start of stimulation. Although the intensity of the arousal responses differed in each case, such arousal responses were seen in all 21 cases and had no relation to emergence or non-emergence from the VS. We defined emergence from the VS as when the VS patient became able to obey our orders or to show an apparent yes by nodding. Eight of the 21 cases emerged from the VS, and could communicate with some speech or other responses, but needed some assistance with their everyday life in bed. Even after long-term rehabilitation, their state of being bedridden remained unchanged in seven of these eight cases. The other case became able to live in a wheelchair. The remaining 13 cases were unable to communicate at all and failed to emerge from the VS. In the eight cases that emerged from the VS following DBS therapy, the Vth wave of the ABR and N20 of the SEP were recorded even with a prolonged latency; continuous EEG frequency analysis demonstrated a desynchronisation pattern or slight desynchronisation pattern; and the pain-related P250 was recorded with an amplitude of over 7 μV. As regards the initial cause of the coma, the cases in whom treatment was effective had suffered brain damage through head injury or cerebrovascular accident, while the three cases of anoxia caused by cardiac arrest were among those in whom treatment was ineffective (Yamamoto et al., 2001, 2003).

Survival period after DBS

A total period of over 10 years follow-up has passed for all 21 DBS cases together, with 4 cases surviving for over 10 years. The survival rate among the 21 cases after the DBS therapy was: 21 cases (100%) at 1 year; 16 cases (76%) at 2 years; 12 cases (57%) at 3 years; 10 cases (48%) at 4 years; 6 cases (29%) at 5 years; 5 cases (24%) at 6 years; 5 cases (24%) at 7 years; 5 cases (24%) at 8 years; 5 cases (24%) at 9 years; and 4 cases (19%) at 10 years. The difference in survival period between the group which recovered ($n = 8$) and the non-recovering group ($n = 13$) was significant ($p < .05$) at over approximately 6 years survival. The causes of death were: infectious disease ($n = 15$), ileus ($n = 1$), and cancer ($n = 1$) (Yamamoto et al., 2003).

Effect of DBS for the MCS

All of the 5 cases of MCS displayed inconsistent behavioural evidence of consciousness before DBS therapy, and they became able to communicate with

definite behavioural responses after the DBS. Four cases emerged from the bedridden state, and were able to enjoy life in their own home. The other case still remained in a bedridden state. Electrophysiological evaluations of these 5 cases revealed the following: the Vth wave of the ABR and N20 of the SEP were recorded even with a prolonged latency; continuous EEG frequency analysis demonstrated a desynchronisation pattern; and the pain-related P250 was recorded with an amplitude of over 7 μV.

DISCUSSION

Selection of the stimulation point

DBS can be effective for achieving emergence from the VS, and an assessment of the possibility of recovery can be made before application of the treatment by checking the patient's neurological status and undertaking electrophysiological evaluations at three months after the initial insult. DBS applied to the mesencephalic reticular formation or CM-pf complex can exert a strong arousal response and elicit marked increases in regional cerebral blood flow and regional cerebral metabolic rate of oxygen (Tsubokawa et al., 1990a,b). In the VS, cerebrocortical functions are more disturbed than brainstem functions, and the relationship between the brainstem and cerebral cortex is important for maintaining consciousness. On this basis, we mainly selected the CM-pf complex for DBS therapy. Electrical stimulation of the CM-pf complex is known to induce incremental recruiting and an augmentory response of the EEG with low-frequency stimulation, and EEG desynchronisation with high-frequency stimulation (Dempsey & Morison, 1942; Jasper, 1955). Luthi and McCormick (1998) have pointed out the importance of the low-threshold calcium spike and H-current in the waxing and waning of the EEG induced by CM-pf complex stimulation.

The DBS therapy for the VS was not sufficiently effective to allow all cases to emerge from the VS. We stress that chronic DBS therapy may be useful for enabling patients to emerge from the VS, if the candidates are selected according to appropriate electrophysiological criteria. These criteria meant that the Vth wave of the ABR and N20 of the SEP were recorded even with a prolonged latency; continuous EEG frequency analysis demonstrated a desynchronisation pattern; or slight desynchronisation pattern; and the pain-related P250 was recorded with an amplitude of over 7 μV. The eight cases that did emerge from the VS were all in a bedridden state for a long period of time, and only one patient recovered sufficiently to live in a wheelchair. In addition to the DBS therapy, we consider that not only the usual rehabilitation care such as physiotherapy but also a special neurorehabilitation programme may be necessary for the treatment of patients in VS.

Selection of the stimulation method

We have usually applied chronic spinal cord stimulation (SCS) for treatment of the MCS and not of the VS. For spinal cord stimulation, PISCES or Quad electrodes (Medtronic Co.) were inserted into the spinal epidural space under fluoroscopy, and stimulation was applied to the upper cervical spinal region. The frequency of stimulation was 5–25 Hz. The stimulation was applied with the minimum stimulation intensity that produced motor responses, and the frequency was selected to induce a motor twitch in each case.

In fact, we have applied DBS for treatment of the MCS in only five cases. In comparison with the VS patients, the MCS patients showed remarkable functional recovery, emerged from the bedridden state, became able to speak correctly, and to enjoy life in their own home. Clinical application of DBS therapy for the MCS is expected to accelerate recovery from this state. In our experience, SCS is also effective for MCS patients. However, there are several points of difference between DBS of the CM-pf complex and SCS. Stimulation of the CM-pf complex can induce a strong arousal response immediately after the start of stimulation; however, SCS cannot induce such a strong arousal response. In neural activation studies employing near infrared spectroscopy (NIRS), stimulation of the CM-pf complex has been shown to elicit marked and long-lasting increases in total haemoglobin and oxy-haemoglobin at the cerebral cortex as compared to SCS.

Time period after the onset of brain injury

We have in practice classified patients into the VS or MCS three months after the onset of brain injury, since most of the spontaneous recovery occurs within the first three months. When we assess the effects of each of the treatments, the most important factor is the time period from the onset of brain injury. The VS diagnosed at one month, three months, or six months after the onset of brain injury constitutes a set of quite different states, and quite different long-term follow-up results tend to be observed. We should therefore stress the time period after the onset of brain injury, when we discuss the long-term follow-up results. We can employ DBS and SCS for treatment of the VS and MCS, and the indications should be considered in the light of neurological and electrophysiological examinations. Not only the classification of the neurological state such as VS or MCS, but also the time period after the onset of brain injury need be taken into account in the treatment of such patients.

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