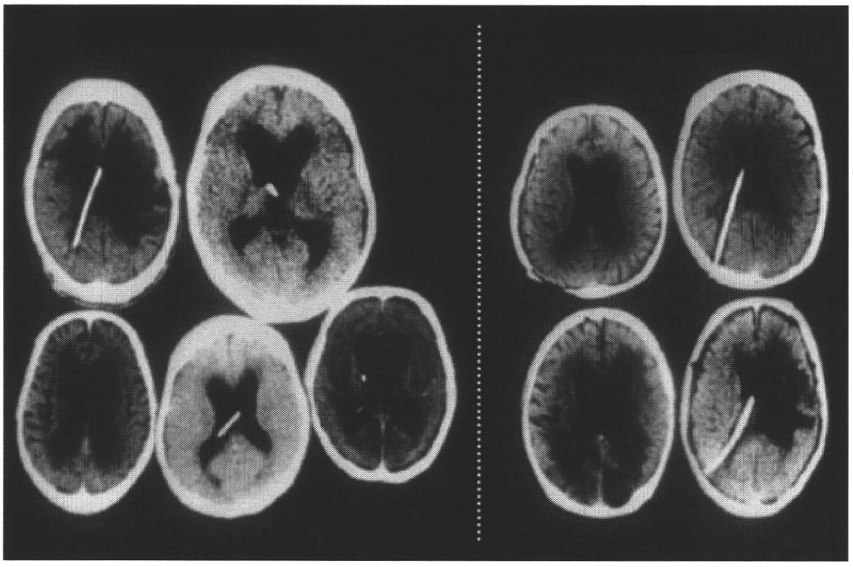

FIG. 6. Results of CT scan carried out before DBS of nine of our patients. After DBS, five patients (left) remained in VS and four patients (right) recovered from VS.

intact or less injured side for electrode implantation, as unilateral stimulation is sufficient to induce a strong arousal response and increase r-CBF in the whole brain.

DBS is not effective for all VS patients as the resting brain function differs between patients. We used the ABR to evaluate brainstem function, the SEP to evaluate thalamocortical function, continuous EEG frequency analysis to estimate the relationship between the brainstem and cerebral cortex, and pain-related P250 to evaluate the higher brain function. Our results revealed that electrophysiological evaluation is very useful for selecting the candidates for DBS, and only 14.9% of VS patients were considered to be candidates for DBS using our criteria. We propose the possibility that chronic DBS may be useful for the recovery of patients from VS, if the candidates are selected on the basis of electrophysiological criteria (Yamamoto *et al.*, 2005; Yamamoto & Katayama, 2005). Figure 6 shows the results of CT scans carried out before DBS in nine of our patients. Four patients recovered from VS and five patients remained in VS, and it was difficult to predict which individuals would recover or fail to recover from VS. CBF is lower in VS patients than in normal subjects, but CBF at the chronic stage of VS does not always represent the severity of acute brain damage. These findings support the importance of electrophysiological evaluation for the treatment of VS.

In our VS patients, we observed a strong arousal response immediately after the start of stimulation, but it took at least 4 months after the start of DBS for the patients to recover from VS. Hassler *et al.* (1969) and Strum *et al.* (1979) started advanced therapy for prolonged coma patients; however, they could not apply chronic DBS. For the first time, Tsubokawa *et al.* (1990a,b) applied chronic DBS for the treatment of VS. For the DBS device, we first used the Extrel system in which the DBS electrode is connected to an internalized radio-frequency receiving device, and the stimulation was performed percutaneously using an external pulse generator. Subsequently we used the Itrel system, which contains an implantable pulse generator, and all the systems could be internalized. Recently, the minimally conscious state (MCS) has been clearly differentiated from VS. Schiff *et al.* (2007) applied bilateral DBS of anterior intralaminar thalamic nuclei and adjacent paralaminar regions of thalamic association nuclei, and reported good results following a 6-month double-blind alternating crossover study in the treatment of an MCS patient. Giacino *et al.* (2002) proposed the concept of MCS, and MCS is characterized by inconsistent but clearly discernible behavioral evidence of consciousness and can be distinguished from coma and VS by the presence of specific behavioral features not found in either of these conditions. MCS is often transient but may also exist as a permanent outcome. They also proposed that recovery from MCS is characterized by a reliable and consistent demonstration of one or both of the following: functional interactive communication and functional use of two different objects.

The Multi-Society Task Force on PVS (1994a,b) reviewed previously reported series of VS patients with traumatic and nontraumatic brain injuries (Braakman *et al.*, 1988; Levin *et al.*, 1991; Sazbon & Groswasser, 1990; Ingvar, 1973; Alberico *et al.*, 1987; Groawasser & Sazbon, 1990). Among 434 adult VS patients 1 month after a severe head injury, 33% had recovered consciousness 3 months after the head injury; this rose to 46% of the total patients at 6 months and 52% at 12 months. Among 169 adult VS patients 1 month after nontraumatic injury, 11% of the total patients had recovered consciousness 3 months after nontraumatic injury, rising to 15% at 6 months, but none of the additional patients had recovered consciousness 12 months after nontraumatic brain injury. Their review indicated that the recovery of consciousness from posttraumatic VS is unlikely after 12 months, and that from nontraumatic VS after 3 months is exceedingly rare.

We have started DBS in VS patients from 4 to 8 months after the onset of comatose brain injury, and recovery from VS occurred after 13 and 10 months for those with head trauma and after 19, 14, 13, 12, 12 and 8 months for those with nontraumatic brain injury. In contrast to their review, the recovery rate of our patients with traumatic head injury treated with DBS was much lower than that of nontraumatic brain injury patients treated with DBS, and only two out of nine patients with traumatic head injury recovered from VS. This recovery rate of patients with traumatic head injury appears to be lower than the spontaneous recovery rate reviewed by The Multi-Society Task Force on PVS. However, most of our traumatic head injury patients were operated on in our department to prevent impending cerebral herniation caused by cerebral contusion with subdural or intracerebral hematoma but, unfortunately, became VS even though their lives were saved. Patients with diffuse brain injury,

namely those patients who sometimes recovered from VS spontaneously before DBS therapy, were not included in our group of VS patients treated with DBS. We have also followed up 18 patients operated on for the treatment of severe head injury who stayed in VS for at least 3 months, and none of these patients recovered from VS spontaneously within 24 months. Although the details of brain injury and resting brain functions in traumatic injury patients whose cases were reviewed by The Multi-Society Task Force on PVS were not provided, we speculate that our traumatic injury patients have different backgrounds from the patients whose cases were reviewed by The Multi-Society Task Force on PVS.

Considering the persistence of physical limitations after the recovery from VS treated with DBS therapy, a specific neurorehabilitation program combined with DBS may be necessary to achieve physical and motor functional recovery and sufficient benefits for VS patients.

## Acknowledgements

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## Abbreviations

ABR, auditory brainstem response; CBF, cerebral blood flow; CM-pf, centromedian–parafascicularis nucleus; DBS, deep brain stimulation; MCS, minimally conscious state; MRF, mesencephalic reticular formation; PVS, persistent VS; r, regional; SEP, somatosensory evoked potential; VS, vegetative state.

## References

Adams, I.E., Hosobuchi, Y. & Fields, H.L. (1974) Stimulation of internal capsule for relief of chronic pain. *J. Neurosurg.*, **41**, 740–744.

Aghajania, G.K. & Vanderman, C.P. (1982) Intracellular identification of central noradrenergic and serotonergic neuron by a new double-labeling procedure. *J. Neurosci.*, **2**, 1786–1792.

Alberico, A.M., Ward, J.D., Choi, S.C., Marmarou, A. & Young, H.F. (1987) Outcome after severe head injury: relationship to mass lesion, diffuse injury, and ICP course in pediatric and adult patients. *J. Neurosurg.*, **67**, 648–656.

Braakman, R., Jennett, W.B. & Minderhound, J.M. (1988) Prognosis of the posttraumatic vegetative state. *Acta Neurochir. (Wien)*, **95**, 49–52.

Bricolo, A., Turazzi, S., Faccioli, F., Odorizzi, F., Sciaretta, G. & Erculiani, P. (1978) Clinical application of compressed spectral array in long-term EEG monitoring of comatose patients. *Electroenceph. Clin. Neurophysiol.*, **45**, 211–225.

Chohadon, F. & Richer, E. (1993) Stimulation cerebrale profonde chez des patients etat vegetatif post traumatique. *Neurochirurgia*, **39**, 281–292.

Dempsey, E.W.A. & Morison, R.S. (1942) A study of thalamocortical relation. *Am. J. Physiol.*, **135**, 291–292.

Dickman, G. (1968) Cortical synchronized and desynchronized responses evoked by stimulation of the putamen and pallidum in cats. *J. Neurol. Sci.*, **7**, 385–391.

Giacino, J.T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D.I., Kelly, J.P., Rosenberg, J.H., Whyte, J., Zafonte, R.D., Zasler, D.O. & Zasler, N.D. (2002) The minimally conscious state: definition and diagnostic criteria. *Neurology*, **58**, 349–353.

Groawasser, Z. & Sazbon, L. (1990) Outcome in 134 patients with prolonged post-traumatic unawareness: part 2: functional outcome of 72 patients recovering consciousness. *J. Neurosurg.*, **72**, 81–84.

Hassler, R., Ore, G.D., Dieckmann, G., Bricolo, A. & Dolce, G. (1969) Behavioural and EEG arousal induced by stimulation of unspecific projection systems in a patient with post-traumatic apallic syndrome. *Electroenceph. Clin. Neurophysiol.*, **27**, 306–310.

Hosobuchi, Y., Adams, J.E. & Rutkin, B. (1973) Chronic thalamic stimulation for the control of facial anesthesia dolorosa. *Arch. Neurol.*, **29**, 158–161.

Ingvar, D.H. (1973) Cerebral blood flow and metabolism in complete apallic syndromes, in states of severe dementia, and in akinetic mutism. *Acta Neurol. Scand.*, **49**, 233–244.

Jasper, H.H., Naquet, R. & King, L.E. (1955) Thalamocortical recruiting responses in sensory receiving areas in the cat. *Electroencephalogr. Clin. Neurophysiol.*, **7**, 99–114.

Jennett, B. & Plum, F. (1972) Persistent vegetative state after brain damage. *Lancet*, **1**, 734–737.

Katayama, Y., Tsubokawa, T., Harano, S. & Tsukiyama, T. (1985) Dissociation of subjective pain report and pain-related late positive component of cerebral evoked potentials in subjects with brain lesions. *Brain Res. Bull.*, **14**, 423–426.

Katayama, Y., Tsubokawa, T., Yamamoto, T., Hirayama, T., Miyazaki, S. & Koyama, S. (1991) Characterization and modification of brain activity with deep brain stimulation in a persistent vegetative state. *Pacing Clin. Electrophysiol.*, **14**, 116–121.

Kayama, Y. & Ogawa, T. (1987) Electrophysiology of ascending, possibly cholinergic neurons in the rat laterodorsal tegmental nucleus, comparison with monoamine neurons. *Neurosci Lett.*, **77**, 277–282.

Kimura, H. & Maeda, T. (1982) Aminergic and cholinergic system in the dorsolateral pontine tegmentum. *Brain Res. Bull.*, **9**, 493–499.

Levin, H.S., Saydjari, C., Eisenberg, H.M., Foulkes, M., Marshall, L.F., Ruff, R.M., Jane, J.A. & Marmarou, A. (1991) Vegetative state after closed head injury: a Traumatic Coma Data Bank Report. *Arch. Neurol.*, **48**, 580–585.

Moruzzi, G. & Magoun, H.W. (1949) Brain stem reticular formation and activation of the EEG. *Electroenceph. Clin. Neurophysiol.*, **1**, 455–473.

Richardson, D.E. & Akil, H. (1977) Pain reduction by electrical brain stimulation in man. Part I: acute administration in periaqueductal and periventricular sites. *J. Neurosurg.*, **47**, 178–183.

Sasaki, K., Staunton, H.P. & Dieckmann, G. (1970) Characteristic features of augmenting and recruiting responses in the cerebral cortex. *Exp. Neurol.*, **26**, 369–392.

Sazbon, L. & Groswasser, Z. (1990) Outcome in 134 patients with prolonged post-traumatic unawareness: part 1; parameters determining late recovery of consciousness. *J. Neurosurg.*, **72**, 75–80.

Schiff, N.D., Giacino, J.T., Kalmar, K., Victor, J.D., Baker, K., Gerber, M., Fritz, B., Eisenberger, B., Connor, J.O., Kobylarz, E.J., Farris, S., Machado, A., McCagg, C., Plum, F., Fins, J.J. & Rezai, A.R. (2007) Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*, **448**, 600–603.

Starzl, T.E., Taylor, C.W. & Magoun, H.W. (1951) Ascending conduction in reticular activating system with special reference to the diencephalons. *J. Neurophysiol.*, **14**, 461–478.

Strum, V., Kuhner, A., Schmitt, P., Assmus, H. & Stock, G. (1979) Chronic electrical stimulation of the thalamic unspecific activating system in a patient with coma due to midbrain and upper brain stem infarction. *Acta Neurochir*, **47**, 235–244.

The Multi-Society Task Force on PVS (1994a) Medical aspects of the persistent vegetative state (first of two parts). *N. Engl. J. Med.*, **330**, 1499–1508.

The Multi-Society Task Force on PVS (1994b) Medical aspects of the persistent vegetative state (second of two parts). *N. Engl. J. Med.*, **330**, 1572–1579.

Tsubokawa, T., Yamamoto, Y. & Katayama, Y. (1990a) Prediction of the outcome of prolonged coma caused by brain damage. *Brain Inj.*, **4**, 329–337.

Tsubokawa, T., Yamamoto, Y., Katayama, Y., Hirayama, T., Maejima, S. & Moriya, T. (1990b) Deep brain stimulation in a persistent vegetative state: follow-up results and criteria for selection of candidates. *Brain Inj.*, **4**, 315–327.

Vincent, S.R., Satoh, K., Armstrong, D.M., Panula, P., Vale, W. & Fibiger, H.C. (1986) Neuropeptides and NADPH-diaphorase activity in the ascending cholinergic reticular system of the rat. *Neuroscience*, **17**, 167–182.

Weinberger, N.M., Velasco, M. & Lundsley, D.B. (1965) Effects of lesions upon thalamically induced electrocortical desynchronization and recruiting. *Electroenceph. Clin. Neurophysiol.*, **18**, 369–377.

Yamamoto, T. & Katayama, Y. (2005) Deep brain stimulation therapy for the vegetative state. *Neuropsychol. Rehabil.*, **15**, 406–413.

Yamamoto, T., Katayama, Y., Oshima, H., Fukaya, C., Kawamata, T. & Tsubokawa, T. (2002) Deep brain stimulation therapy for a persistent vegetative state. *Acta Neurochir. (Suppl.)*, **79**, 79–82.

Yamamoto, T., Katayama, Y., Kobayashi, K., Kasai, M., Oshima, H. & Fukaya, C. (2003) DBS therapy for a persistent vegetative state: ten years follow-up results. *Acta Neurochir. (Suppl.)*, **87**, 15–18.

Yamamoto, T., Katayama, Y., Kano, T., Kobayashi, K., Oshima, H. & Fukaya, C. (2004) Deep brain stimulation for the treatment of Parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity. *J. Neurosurg.*, **101**, 201–209.

Yamamoto, T., Katayama, Y., Kobayashi, K., Oshima, H., Fukaya, C. & Katayama, Y. (2005) DBS therapy for the vegetative state and minimally conscious state. *Acta Neurochir. Suppl.*, **93**, 101–104.

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# Direct Relief of Levodopa-Induced Dyskinesia by Stimulation in the Area Above the Subthalamic Nucleus in a Patient With Parkinson's Disease

## —Case Report—

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### Abstract

**A 71-year-old woman with a 25-year history of levodopa (LD)-responsive Parkinson's disease (PD) developed on-off motor fluctuation and severe peak dose dyskinesia. She underwent deep brain stimulation of the subthalamic nucleus (STN-DBS). STN-DBS induced attenuation of her cardinal PD symptoms and marked improvement of dyskinesia without reduction of LD dosage perioperatively. STN-DBS thus markedly attenuated the cardinal symptoms of PD. LD-induced dyskinesia can also be controlled via reduction of LD dosage as an indirect effect of STN-DBS. The present case provides evidence of the direct antidyskinetic effect of STN-DBS, and suggests that LD-induced dyskinesia can be inhibited by stimulation in the area above the STN.**

Key words: deep brain stimulation of subthalamic nucleus, dyskinesia, Parkinson's disease, antidyskinetic effect, area above subthalamic nucleus

### Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) induces attenuation of the cardinal symptoms of Parkinson's disease (PD) during off-periods as well as dopa-induced dyskinesia.[4,9,11-13] Relief of dopa-induced dyskinesia after STN-DBS is believed to depend on postoperative reduction of dopaminergic medication,[6] but STN-DBS may directly decrease dopa-induced dyskinesia.[1,5,10,14] We describe a patient with PD whose dopa-induced dyskinesia improved after STN-DBS.

### Case Report

A 71-year-old woman with a 25-year history of levodopa (LD)-responsive PD developed on-off motor fluctuation and peak dose dyskinesia with an LD dose of 500 mg/day. She had suffered fracture of her left femur 11 years previously and had difficulty with ambulation due to contracture of her left lower extremity. About 30–60 minutes after each administration of LD, choreiform dyskinesia developed and persisted for 1 hour. Motor score on the United Parkinson's Disease Rating Scale (UPDRS) motor score was 38 in the off-condition and 28 in the on-condition. Dyskinesia score (six body parts, each scored 0–4, maximum score 24) was 17 in the on-condition.

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Bilateral STN-DBS was performed. She continued to receive medication perioperatively, except on the day of the procedure. A tentative target was determined based on magnetic resonance (MR) imaging using human brain atlas software, single- and multi-unit extracellular recording, and microstimulation. Model 3387 DBS electrodes were implanted under microelectrode guidance without complications. The electrodes were directed from the frontal burr hole at an angle of 50° to the horizontal plane.

Postoperative MR imaging demonstrated correct placement of the electrodes (Fig. 1). Two of the four contacts (contacts 0 and 1) were within the STN. Contacts 2 and 3 were located in the area above the STN including the Forel H field and the zona incerta. While receiving the same doses of antiparkinsonian drugs as preoperatively, the patient underwent monopolar stimulation using contacts 0 to 3 as the cathode and a case as the anode. However, dysarthria was observed using all contacts under low amplitude. Then she underwent bipolar stimulation using contacts 0 to 2 as the cathode and contact 3 as the anode. The intensity and frequency of stimulation were 1.8 V and 135 Hz, respectively, and the pulse width was 150 μsec. No adverse effect was observed under these conditions. Using contact 0 or 1 as the cathode, her cardinal Parkinson sym-

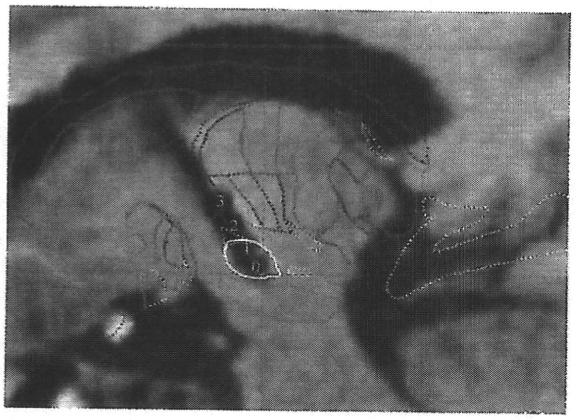

**Fig. 1 Postoperative $T_1$-weighted magnetic resonance image showing contacts placed in the subthalamic nucleus and the area above this nucleus.**

**Table 1 Correlation between position of the cathode and symptoms under bipolar stimulation**

| Cathode contact | Rigidity | Tremor | Akinesia | Dyskinesia |
|---|---|---|---|---|
| 0 | ↓ | ↓ | ↓ | → |
| 1 | ↓ | ↓ | ↓ | → |
| 2 | ↓ | ↓ | ↓ | ↓↓ |

Anode was contact 3. →: no change, ↓: decrease, ↓↓: large decrease.

ptoms were improved, although LD-induced dyskinesia remained unchanged. In contrast, using contact 2 as the cathode, both LD-induced dyskinesia and cardinal Parkinson symptoms were markedly attenuated (Table 1). The dose of LD was gradually reduced, and the patient eventually received only dopamine agonist (cabergoline, total dose 1.0 mg/day). The postoperative UPDRS motor score was 27 and the dyskinesia score was 0.

## Discussion

The antidyskinetic effect of STN-DBS is due to the postoperative reduction of LD intake.[3,7,15] In contrast, DBS of the globus pallidus internus (GPi) has a direct antidyskinetic effect.[16] GPi-DBS yields significant improvement of LD-induced dyskinesia after surgery without reduction of LD dosage. In our case, bipolar stimulation for STN-DBS using contacts 0 or 1 as the cathode induced attenuation of cardinal PD symptoms but not LD-induced dyskinesia, whereas bipolar stimulation using contact 2 as the cathode induced attenuation of both cardinal PD symptoms and LD-induced dyskinesia without reduction of LD dosage. These findings suggest that stimulation in the area above the STN inhibited LD-induced dyskinesia, consistent with previous findings.[1,5,8,10,14] Pallidothalamic, pallidosubthalamic, and subthalamopallidal fibers are densely distributed in the area above the STN.[10] Furthermore, a study using tracer techniques in the squirrel monkey demonstrated that pallidothalamic fibers originating within the sensorimotor region of the GPi mainly project through the lenticular fasciculus, running through the area above the STN.[2] Stimulation of these fibers may have effects similar to GPi-DBS and thus inhibit dopa-induced dyskinesia.

## References


1) Alterman RL, Shils JL, Gudesblatt M, Tagliati M: Immediate and sustained relief of levodopa-induced dyskinesia after dorsal relocation of a deep brain stimulation lead. Case report. *Neurosurg Focus* 17(1): E6, 2004
2) Baron MS, Sidibe M, Delong MR: Course of motor and associative pallidothalamic projections in monkeys. *J Comp Neurol* 429: 490–501, 2001
3) Benabid AL, Benazzouz A, Limousin P, Koudsie A, Krack P, Piallat B, Pollak P: Dyskinesias and the subthalamic nucleus. *Ann Neurol* 47: S189–192, 2000
4) Burchiel KJ, Anderson VC, Favre J, Hammerstad JP: Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. *Neurosurgery* 45: 1375–1382, 1999
5) Figueiras-Mendez R, Marin-Zarza F, Antonio Molina J, Jimenez-Jimenez FJ, Orti-Pareja M, Magarinos C, Lopez-Pino MA, Martinez V: Subthalamic nucleus stimulation improves directly levodopa induced dyskinesias in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 66: 549–550, 1999
6) Follett KA: Comparison of pallidal and subthalamic deep brain stimulation for the treatment of levodopa-induced dyskinesias. *Neurosurg Focus* 17(1): E3, 2004
7) Fraix V, Pollak P, Van Blercom N, Xie J, Krack P, Koudsie A, Benabid AL: Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia in Parkinson's disease. *Neurology* 55: 1921–1923, 2000
8) Herzog J, Pinsker M, Wasner M, Steigerwald F, Wailke S, Deuschl G, Volkmann J: Stimulation of subthalamic fibre tracts reduces dyskinesias in STN-DBS. *Mov Disord* 22: 679–684, 2007
9) Katayama Y, Kasai M, Oshima H, Fukaya C, Yamamoto T, Ogawa K, Mizutani T: Subthalamic nucleus stimulation for Parkinson disease: benefits observed in levodopa-intolerant patients. *J Neurosurg* 95: 213–221, 2001
10) Katayama Y, Oshima H, Kano T, Kobayashi K, Fukaya C, Yamamoto T: Direct effect of subthalamic nucleus stimulation on levodopa-induced peak-dose dyskinesia in patients with Parkinson's disease. *Stereotact Funct Neurosurg* 84: 176–179, 2006
11) Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A, Benabid AL: Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. *Brain* 121(Pt 3): 451–457, 1998
12) Kumar R, Lozano AM, Kim YJ, Hutchison WD, Sime E, Halket E, Lang AE: Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology* 51: 850–855, 1998
13) Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A: Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. *Neurology* 53: 85–90, 1999
14) Oshima H, Kobayashi K, Kasai M, Fukaya C, Yamamoto T, Katayama Y: [Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia]. *Kinoteki No Shinkei Geka* 42: 49–52, 2003 (Jpn, with Eng abstract)

15) Russmann H, Ghika J, Combrement P, Villemure JG, Bogousslavsky J, Burkhard PR, Vingerhoets FJG: L-dopa-induced dyskinesia improvement after STN-DBS depends upon medication reduction. *Neurology* 63: 159–155, 2004
16) Volkmann J, Sturm V, Weiss P, Kappler J, Voges J, Koulousakis A, Lehrke R, Hefter H, Freund HJ: Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. *Ann Neurol* 44: 953–961, 1998

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Case Report

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# Thalamic Deep Brain Stimulation for the Treatment of Action Myoclonus Caused by Perinatal Anoxia

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**Key Words**
Myoclonus · Deep brain stimulation · Thalamus · Perinatal anoxia

**Abstract**
***Background:*** Perinatal anoxia rarely causes myoclonus as the main neurologic abnormality. The exact neuronal mechanism underlying myoclonus induced by perinatal anoxia remains unknown. Some studies have indicated that the development of involuntary movements may be related to the maturation of the thalamus after birth. ***Objectives and Methods:*** Here, we describe the first case of a patient who developed action myoclonus after experiencing perinatal anoxia and was successfully treated by chronic deep brain stimulation (DBS) of the thalamus (thalamic DBS). ***Results and Conclusion:*** The effectiveness of chronic thalamic DBS in this patient supports the concept of involvement of the thalamus in postperinatal anoxic myoclonus.



## Introduction

Myoclonus is rarely the main neurologic sequela of perinatal anoxia [1–3]; it is more commonly observed after brain anoxia in adults [1–3]. Deep brain stimulation (DBS) of the thalamus (thalamic DBS) is effective for the treatment of tremors [4–13]. Furthermore, thalamic DBS has been reported to effectively control various other involuntary movements such as hemiballismus [8, 14], writer's cramp [15] (which is a type of dystonia) and chorea associated with a case of cerebral palsy [16]. This treatment has also been found to ameliorate myoclonic symptoms in patients with inherited myoclonus dystonia syndrome [17–19]. However, the effectiveness of DBS for the treatment of myoclonus induced by perinatal anoxia has not yet been studied. We report here the case of a patient who developed action myoclonus as a result of perinatal anoxia and was successfully treated by thalamic DBS.

## Case Report

*Patient History*

A 36-year-old right-handed man presented with marked aggravation of involuntary movements. The patient had a history of perinatal hypoxia and was diagnosed as having floppy infant syn-

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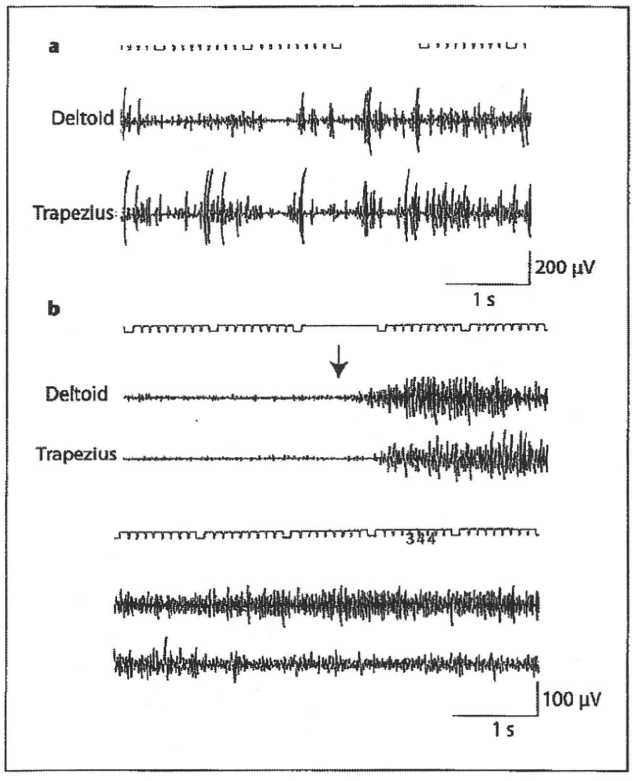


**Fig. 1.** Surface electromyography (EMG) of the deltoid and trapezius in the present patient. **a** Before surgery; recording of the patient attempting to hold his left arm in front of him. **b** After surgery; recording during thalamic stimulation. The arrow indicates the point at which the patient started to hold his left arm out in front of him. (Note: the EMG amplitude scale differs between **a** and **b**.)

drome at birth. He had an unsteady gait due to hypotonia of the muscles of the lower limbs and required an orthotic for walking between the ages of 12 and 18 months. He was diagnosed as having cerebral palsy at 18 months of age. He developed slight involuntary movements of both his upper limbs at 4 years of age. At 13 years of age, these involuntary movements became markedly aggravated; they subsequently progressed to jerky movements and have worsened steadily with advancing age. He has undergone treatment with several drugs, without any obvious effect. He was therefore finally referred to our hospital for DBS surgery at 36 years of age.

On examination, jerky movements of both upper limbs, mainly the proximal limbs, were observed, with no cerebellar signs such as hypotonia or hand ataxia. The involuntary movements appeared occasionally at rest. The finger-to-nose test aggravated the involuntary movements without ataxia. The involuntary movements were stereotyped. Electromyography using surface electrodes revealed irregular and repetitive burst discharges when the patient performed any action, particularly elevation of the arm or holding a cup (fig. 1a). The item of severity of myoclonus with action of the arm on the Unified Myoclonus Rating Scale (UMRS) [20] was employed to evaluate the action myoclonus. This item is scored as the product of scores for the frequency and amplitude of myoclonus with action. The frequency of myoclonus is scored as follows: no jerks per 10 s, 0; ≤1 jerk per 10 s, 1; 2 or 3 jerks per 10 s, 2; 4–9 jerks per 10 s, 3; ≥10 jerks per 10 s, 4. The amplitude of the worst myoclonus seen on finger-to-nose testing is scored using the following procedure: ask the patient to hold both arms forward with the palms down for 10 s, then ask the patient to extend both wrists for 10 s, then perform the finger-to-nose test 4 times and finally, ask the patient to finish by leaving his finger on his nose for 10 s. The movement is scored as follows: zero, 0; trace movement only, 1; small-amplitude jerks, easily visible (<25% of maximum possible movement), 2; moderate-amplitude jerks (25–75% of maximum possible movement), 3; large-amplitude jerks (near maximum movement), 4. The score for the severity of myoclonus with action of the arm on the UMRS was 12 for the left arm and 9 for the right arm.

Magnetic resonance (MR) imaging of the brain revealed slight brain atrophy, without any other abnormalities. The involuntary movements improved at rest and disappeared during sleep. There was no known family history of movement disorder or other neurological disease. We made plans to conduct surgery on the patient for implantation of a DBS electrode to treat the myoclonus, and obtained the informed consent of the patient and his family. We did not schedule the performance of bilateral surgery at one time because we needed to confirm the effectiveness of DBS for the patient. We therefore planned the introduction of an electrode in the right thalamus first, since the involuntary movements of the left hand were worse than those of the right hand.

*Surgical Procedure*

The surgical procedure was planned using MR images. Following the administration of a local anesthetic, a Leksell G head frame (Elekta Instruments AB) was applied to the patient's head. The anterior commissure (AC) and posterior commissure (PC) were identified using Leksell SurgiPlan® (Elekta Instruments AB), a customized software program for functional stereotaxy. An X-ray indicator (Elekta Instruments AB) was also employed to identify the AC and PC on plain X-ray films. A burr hole was made approximately 2.0 cm anterior to the coronal suture and approximately 2.5 cm lateral to the midline. Extracellular single- and multiunit recordings were obtained using a semimicroelectrode (0.4 MΩ). With the intention of identifying the anterior border of the nucleus ventrocaudalis (Vc), which constitutes the nucleus ventralis intermedius (Vim)-Vc border, we directed the first trajectory of the semimicroelectrode utilized for extracellular unit recording toward the anterior aspect of the PC in lateral view and at the level of the AC-PC line and 14.5 mm lateral to the midline. Neuronal activity was also fed into an audiospeaker. The neuronal activity was examined under various conditions such as somatic sensory stimulation and active movements. Neurons that were activated in response to somatic sensory stimulation, that is, in response to passive joint movements of the contralateral limb without a response in skin deformation caused by the stimuli, were classified as (1) deep sensory cells; and neurons that responded to light touch on the skin of the face and contralateral limbs were classified as (2) cutaneous sensory cells. The Vim-Vc border was defined physiologically as the anterior-most neurons along a trajectory which was mapped such that >50% of the neu-

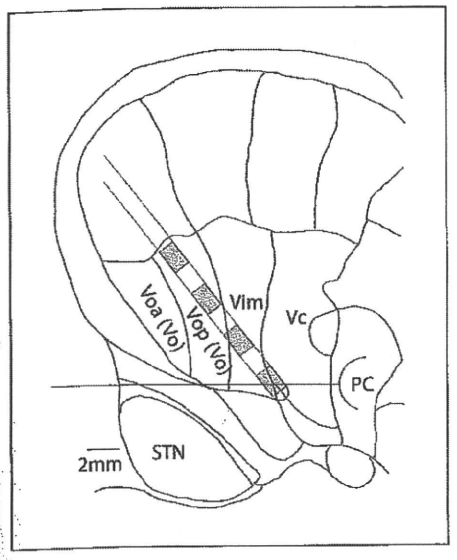


**Fig. 2.** Anatomical relationship between the thalamic nucleus and DBS electrode. **a** A 14.5-mm lateral section from the Schaltenbrand-Wahren human brain atlas with the AC-PC length stretched to fit the coordinates obtained from the patient's stereotactic magnetic resonance images. STN = Subthalamic nucleus; Voa = nucleus ventralis oralis anterior; Vop = nucleus ventralis oralis posterior.

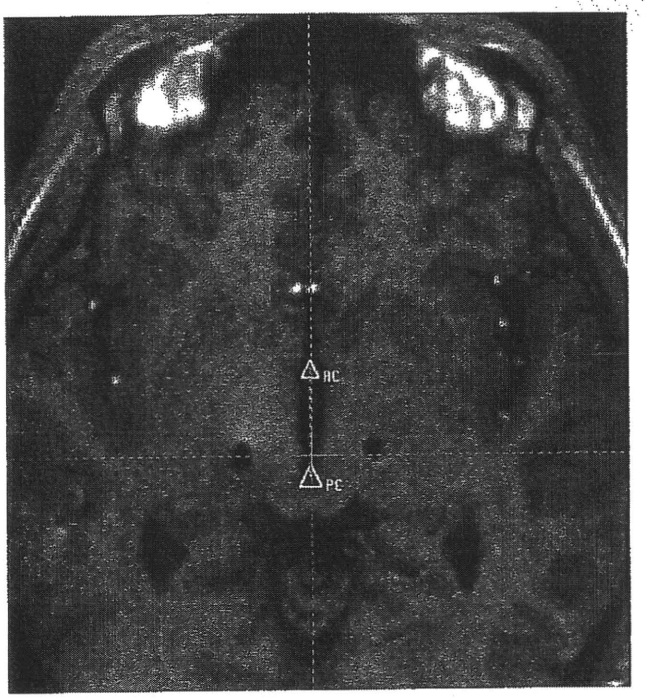


**Fig. 3.** Location of bilateral DBS electrodes on magnetic resonance (MR) imaging. Postoperative $T_1$-weighted axial MR imaging of the brain revealed the lead locations at the level of the AC-PC commissural plane. The leads are visualized as dark circular spots in the brain parenchyma.

rons located posterior to the trajectory were either deep or cutaneous sensory neurons [21]. On the basis of observations made during our initial trajectory assessment, the Vim-Vc border was identified as a vertical line approximately 3 mm anterior to the PC. This identification was consistent with the Vim-Vc border determined based on the Schaltenbrand-Wahren atlas. The second trajectory of the semimicroelectrode was directed toward a position on the Vim-Vc border at the level of the AC-PC line, 14.5 mm lateral to the midline. The target was approached through the burr hole at an angle of 52° to the horizontal plane of the AC-PC line. Subsequently, the DBS electrode (model 3387; Medtronic Inc., Minn., USA) was implanted through the second trajectory using stereotactic instruments, and a test stimulation was conducted with the DBS electrode in place. This electrode has 4 contacts that are numbered sequentially from 0 to 3, with the most distal contact being 0 and the most proximal contact being 3. Each contact is 1.5 mm long, and the contacts are spaced 1.5 mm apart. The DBS electrode was implanted to cover a wide region of the thalamus, including not only the Vim but also the nucleus ventralis oralis (Vo).

Contact 0 was located at the Vim-Vc border; contact 1 in the central part of the Vim, and contacts 2 and 3 within the Vo (fig. 2). Test stimulations were performed for 4 days after completion of the procedure to confirm myoclonus suppression (fig. 1b). The stimulations showed that satisfactory control of the involuntary movements had been achieved. Therefore, under general anesthesia, an internal pulse generator (Soletra; Medtronic) was placed in an infraclavicular pocket and connected subcutaneously to the DBS lead. After 2 weeks, another DBS electrode was implanted into the left Vo/Vim, and a pulse generator was also implanted using the method described above (fig. 3).

*Postoperative Outcome*

After the operations, we assessed the most effective combination of contacts of the electrode at a frequency of 135 Hz and a pulse width of 0.21 ms. The voltage of stimulation was increased to an upper limit where such adverse effects as paresthesia began to appear. The effect of stimulation was evaluated with blinded contact combinations.

The following combinations stimulated mainly the Vim (fig. 2): contact 0 as the anode (+) and contact 1 as the cathode (–), contact 1 as the cathode (–) and contact 2 as the anode (+), and monopolar stimulation using contact 1 as the cathode (–); these combinations had some effect on the myoclonus. However, the strongest effect was achieved when contact 1 was the cathode (–) and contact 3 was the anode (+); this combination activated a wide area extending from the Vo to the Vim. When contact 0 located in the Vc was used as the cathode (–), paresthesia was evoked by a low intensity of stimulation. The optimal combinations were the same on both sides. At the 24-month follow-up, the item of severity of myoclonus with action of the arm on the UMRS score was reduced from 12/16 to 2/16 for the left arm and from 9/16 to 2/16 for the right arm (table 1).

**Table 1.** Efficacy of thalamic DBS for myoclonus

| Severity of myoclonus with action of the arm on the UMRS | Left arm | | Right arm | |
|---|---|---|---|---|
| | before surgery | after surgery | before surgery | after surgery |
| Total score (frequency × amplitude) | 12 | 2 | 9 | 2 |
| Frequency | 4 | 2 | 3 | 2 |
| Amplitude | 3 | 1 | 3 | 1 |

The combination of electrode contacts used was as follows: contact 1 as the cathode (–) and contact 3 as the anode (+).

Scores are between 0 (best) and 4 (worst) for frequency and amplitude and between 0 (best) and 16 (worst) for total.

## Discussion

Perinatal anoxia can, on rare occasions, induce myoclonus as the main neurologic abnormality [1–3]. The detailed pathophysiology of postperinatal anoxic myoclonus remains unknown. Some reports have suggested that the symptoms of myoclonus after perinatal anoxia of the ascending efferents of the basal ganglia to the thalamus and the thalamocortical pathways are not observed in the first decade of life, despite the development of pathological lesions specific to these symptoms [22, 23]. Moreover, Sugama and Kusano [3] suggested that the development of movement disorder due to perinatal anoxia may be related to the maturation of the thalamus after birth. Our patient could thus have been in a thalamotomy-like state during the infantile period because of the immaturity of the thalamus. With advancing age, various involuntary movements develop after the maturation of the thalamus [3]. The effectiveness of chronic thalamic DBS in our patient may provide support for the concept of involvement of the thalamus in postperinatal anoxic myoclonus.

Recently, it has been reported that thalamic DBS ameliorated myoclonus in a patient with myoclonus dystonia syndrome; this patient did not have a history of perinatal anoxia [17–19]. The optimal site for thalamic DBS remains to be determined. Although the exact mechanisms underlying myoclonus are not understood, a study on monkeys has indicated that dysfunction of the Vim in the thalamus may play a role in the generation of myoclonic jerks [24]. In our patient, however, the most effective stimulation site covered a wide area that included the Vo in addition to the Vim. Tremor suppression is generally attributed to stimulation of the Vim but has been reported to follow stimulation of the Vo [25] or a wide area centered on the Vim and including the Vo [26]. In the large series of cases presented by Benabid et al. [4], the optimal tremor control site was located 4–8 mm anterior to the PC and 0–2 mm superior to the AC-PC line. From these coordinates, we infer that the areas stimulated by spread of the electrical current included not only the Vim but also the Vo [27]. Consistent with our findings, Trottenberg et al. [19] suggested that the effect of thalamic stimulation on myoclonus in myoclonus dystonia syndrome may be attributable to electrophysiological ablation of the Vo and Vim or nearby fiber systems.

## Conclusions

We successfully treated a patient with severe action myoclonus due to perinatal anoxia by thalamic DBS. Such thalamic DBS may offer an effective and safe treatment modality for intractable postperinatal anoxic myoclonus.

## References


1 Obeso JA, Lang AE, Rothwell JC, Marsden CD: Postanoxic symptomatic oscillatory myoclonus. Neurology 1983;33:240–243.

2 Rondot P, Said G, Ferrey G: Volitional hyperkinesia: electrological study: classification. Rev Neurol (Paris) 1972;126:415–426.

3 Sugama S, Kusano K: A case of dyskinetic cerebral palsy resembling post-anoxic action myoclonus. Brain Dev 1995;17:210–212.

4 Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, Payen I, Benazzouz A: Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 1996;84:203–214.

5 Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J: Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991; 337:403–406.

6 Blond S, Caparros-Lefebvre D, Parker F, Assaker R, Petit H, Guieu JD, Christiaens JL: Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. J Neurosurg 1992;77:62–68.

7 Caparros-Lefebvre D, Blond S, Vermersch P, Pecheux N, Guieu JD, Petit H: Chronic thalamic stimulation improves tremor and levodopa-induced dyskinesias in Parkinson's disease. J Neurol Neurosurg Psychiatry 1993; 56:268–273.

8 Katayama Y, Fukaya C, Yamamoto T: Control of poststroke involuntary and voluntary movement disorders with deep brain or epidural cortical stimulation. Stereotact Funct Neurosurg 1997;69:73–79.
9 Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R: Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord 2001;16:464–468.
10 Limousin P, Speelman JD, Gielen F, Janssens M: Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 1999; 66:289–296.
11 Nguyen JP, Degos JD: Thalamic stimulation and proximal tremor: a specific target in the nucleus ventrointermedius thalami. Arch Neurol 1993;50:498–500.
12 Yamamoto T, Katayama Y, Kano T, Kobayashi K, Oshima H, Fukaya C: Deep brain stimulation for the treatment of parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity. J Neurosurg 2004;101: 201–209.
13 Yamamoto T, Katayama Y, Fukaya C, Oshima H, Kasai M, Kobayashi K: New method of deep brain stimulation therapy with two electrodes implanted in parallel and side by side. J Neurosurg 2001;95:1075–1078.
14 Katayama Y, Yamamoto T, Kobayashi K, Oshima H, Fukaya C: Deep brain and motor cortex stimulation for post-stroke movement disorders and post-stroke pain. Acta Neurochir Suppl 2003;87:121–123.
15 Fukaya C, Katayama Y, Kano T, Nagaoka T, Kobayashi K, Oshima H, Yamamoto T: Thalamic deep brain stimulation for writer's cramp. J Neurosurg 2007;107:977–982.
16 Thompson TP, Kondziolka D, Albright AL: Thalamic stimulation for choreiform movement disorders in children: report of two cases. J Neurosurg 2000;92:718–721.
17 Kuncel AM, Turner DA, Ozelius LJ, Greene PE, Grill WM, Stacy MA: Myoclonus and tremor response to thalamic deep brain stimulation parameters in a patient with inherited myoclonus-dystonia syndrome. Clin Neurol Neurosurg 2009;111:303–306.
18 Kupsch A, Trottenberg T, Meissner W, Funk T: Neurostimulation of the ventral intermediate thalamic nucleus alleviates hereditary essential myoclonus. J Neurol Neurosurg Psychiatry 1999;67:415–416.
19 Trottenberg T, Meissner W, Kabus C, Arnold G, Funk T, Einhaupl KM, Kupsch A: Neurostimulation of the ventral intermediate thalamic nucleus in inherited myoclonus-dystonia syndrome. Mov Disord 2001;16:769–771.
20 Frucht SJ, Leurgans SE, Hallett M, Fahn S: The unified myoclonus rating scale. Adv Neurol 2002;89:361–376.
21 Hua SE, Lenz FA: Posture-related oscillations in human cerebellar thalamus in essential tremor are enabled by voluntary motor circuits. J Neurophysiol 2005;93:117–127.
22 Segawa M: Pathophysiologies of dystonia and myoclonus: consideration from the standpoint of treatment. Rinsho Shinkeigaku 1995;35:1390–1393.
23 Segawa M: Development of the nigrostriatal dopamine neuron and the pathways in the basal ganglia. Brain Dev 2000;22(suppl 1): S1–S4.
24 Guehl D, Burbaud P, Boraud T, Bioulac B: Bicuculline injections into the rostral and caudal motor thalamus of the monkey induce different types of dystonia. Eur J Neurosci 2000;12:1033–1037.
25 Hassler R, Mundinger F, Riechert T: Stereotaxis in Parkinson Syndrome. Clinical-Anatomical Contributions to Its Pathophysiology. New York, Springer, 1979.
26 Strafella A, Ashby P, Munz M, Dostrovsky JO, Lozano AM, Lang AE: Inhibition of voluntary activity by thalamic stimulation in humans: relevance for the control of tremor. Mov Disord 1997;12:727–737.
27 Starr PA, Vitek JL, Bakay RA: Ablative surgery and deep brain stimulation for Parkinson's disease. Neurosurgery 1998;43:989–1013; discussion 1013–1015.

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特集／脳の可塑性とリハビリテーションへの応用

# 大脳電気刺激と脳の可塑性

山本隆充[*1]　深谷　親[*2]　片山容一[*3]

Abstract　大脳皮質運動野刺激の電極留置には，cortico-spinal motor evoked potential (cortico-spinal MEP)を用いる方法が有用である．全身麻酔下でも安定した記録が可能で，最適の刺激部位を決定するための電極位置の微量調整も可能である．運動機能回復を目的とした大脳皮質運動野刺激が報告されているが，これらの報告は3週あるいは6週間のリハビリテーションと同時に大脳皮質運動野刺激を行い，その後に刺激装置を抜去するもので，長期間の慢性刺激についての検討はされていない．今回の研究では，6か月以上の運動野の慢性刺激で運動機能が改善することが明らかとなった．しかし，刺激条件の設定が重要であり，持続的に長時間の刺激を行うと逆に運動機能を悪化させることが明らかとなった．これらの事実から，運動機能の回復を目的とした大脳皮質運動野刺激で運動閾値の80％の刺激強度を用いた場合には，1日の刺激を3時間程度に制限する必要があると結論された．

Key words：運動誘発電位(motor evoked potential)，大脳皮質運動野刺激(motor cortex stimulation)，運動麻痺(motor weakness)，神経リハビリテーション(neurorehabilitation)，脳深部刺激療法(deep brain stimulation)

## はじめに

各種の振戦に対する視床(Vop/Vim核)刺激[1]，パーキンソン病に対する視床下核刺激[2]，ジストニアに対する淡蒼球内節刺激[3]などの脳深部刺激療法の有効性が報告されている．これらの刺激部位では，破壊によっても程度の差は認めるも同様の効果を発揮することができる．また振戦に対する視床(Vop/Vim核)刺激に低頻度刺激を用いると振戦がかえって増悪し，100 Hz以上の高頻度刺激で完全に振戦を制御することができる(図1)．このような事実から，脳深部刺激療法では刺激部位に伝達される異常神経活動を抑制(脱分極性ブロック)することにより，大脳皮質–基底核–視床の運動回路機能を改善することが主たる効果発現機序であると考えられている．一方，幻肢痛に対する視床知覚中継核(Vc核)刺激では，刺激の継続によって必要な刺激時間が序々に減少し，刺激の中止によって再度必要な刺激時間が増加することから[4]，脳深部刺激療法は神経機構の再構築(可塑性)にも有効であり，これらの機序が混在しているものと考えられる．

脳卒中後疼痛(post-stroke pain)に対する大脳皮質運動野慢性電気刺激療法は，本邦で開発された治療法である[5)~7)]．現在は，世界各国で臨床応用され，その有効性が確認されるとともに，各種の神経障害性疼痛の治療に広く用いられるようになった[8)~10)]．我々が，これまでに視床痛やワレンベルグ症候群などの脳卒中後疼痛の治療を目的として大脳皮質運動野刺激を行った症例のなかに，四肢ならびに顔面の運動麻痺や発声が改善する症例を数多く経験し，この事実を報告してきた[7)]．

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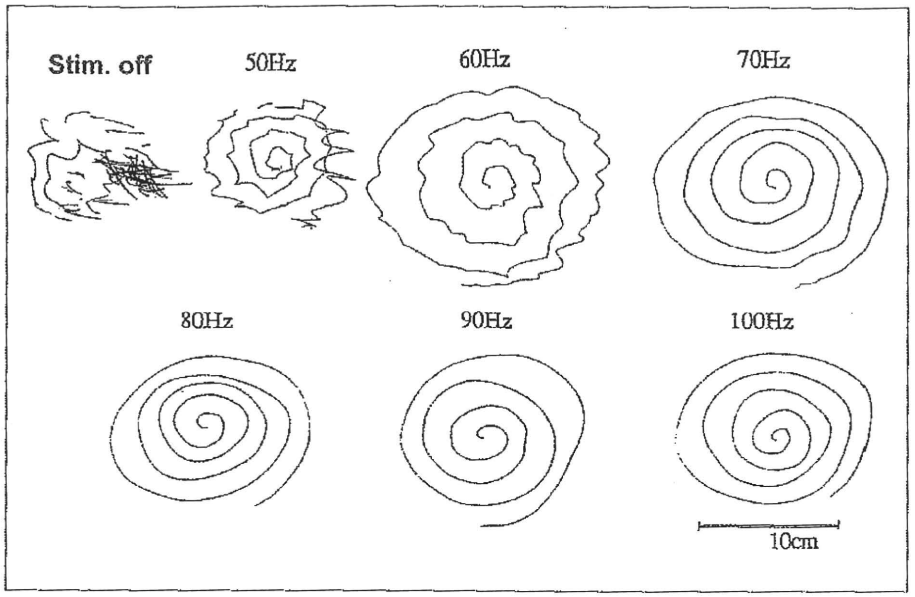


**図 1.**
振戦制御のための視床(Vim/Vop 核)刺激
振戦を完全に制御するためには，100 Hz 以上の高頻度刺激を用いる必要がある．

本稿では，脳卒中後疼痛の治療を目的とした大脳皮質運動野刺激を行い，同時に運動機能障害の改善について検討した結果について紹介する．さらに，大脳皮質運動野刺激における最適な電極留置部位の決定法と刺激条件についても紹介する．

## 運動麻痺の改善についての検討症例

対象は脳卒中発症後既に 1 年以上経過している 6 例で，全例で四肢の疼痛と運動麻痺を認めた．これらの症例は，いずれもドラッグチャレンジテスト[6]におけるケタミンテストで，visual analogue scale(VAS)が 40%以上減少する症例である．

## ドラッグチャレンジテスト

我々の用いているドラッグチャレンジテストは，visual analogue scale(VAS)で痛みの評価を行い，薬物投与による VAS の変化を比較している．この評価法の特徴は，プラセボ投与から始め，少量ずつ段階的に薬物を投与するので，少量から連続的に多量投与までの効果を確認できることである．患者の訴える疼痛がどのような薬物にどの程度の投与量でどの程度反応するか，または全く反応しないかを明らかにすることができる．また，ketamine-sensitive な症例では，脳脊髄刺激療法に低用量ケタミン点滴療法を併用することによって，除痛効果を高めることができる[11]．ケタラールテストは，5 分間隔で生食を 2 回投与後，同様に 5 分間隔で ketamine hydrochloride を 5 mg，合計 25 mg まで静脈内投与する[6]．(薬物投与後の VAS÷薬物投与前の VAS)×100%＝% VAS として，% VAS が 60%以下となったもの，すなわち薬物投与前と比較して，VAS が 40%以上減少したものを sensitive case，40%以下のものを resistant case としている．

## 大脳皮質運動野刺激の刺激部位決定

大脳皮質運動野刺激には，MR imaging を用いた画像誘導装置と cortico-spinal motor evoked potential(cortico-spinal MEP)を用いて，電極の留置部位を決定した[12]．cortico-spinal MEP は大脳皮質を直接に電気刺激し，頸椎硬膜外から下行性の脊髄誘発電位を記録する方法で，通常の全身麻酔下，筋弛緩剤使用の状態で記録が可能である．最初に出現する陰性波は皮質下の錐体路ニューロンが直接に刺激された反応で D 波，これに続く多峰性の陰性波は皮質内の介在ニューロンを介する反応で I 波と呼ばれる．I 波は麻酔で抑制されるが，D 波は抑制されないことから，術中のモニタリングの指標として最適である[13]．

図 2 に示すように，多連円盤電極の 1 番目の刺激点は中心溝のすぐ後方，2 番目の刺激点は中心前回の後半部，3 番目の刺激点は中心前回の前半部，4 番目の刺激点は中心前溝の前方に位置する．1〜4 番までの隣合う刺激点を用いて，電極間距離 10 mm で双極刺激を行うと，中心前回後半部の陽

極刺激によって，最も低い閾値でD波が誘発された．しかし，中心前溝の前に位置する刺激点では，50 mAの陽極刺激を用いてもD波は誘発されなかった．電極間距離10 mmで双極刺激を行うと，D波を誘発する部位は周囲から明確に区別することができる．また，陰極刺激よりも陽極刺激のほうがD波を弱い刺激で誘発可能であることが明らかとなった[14]．

刺激電極にはメドトロニック社製のRESUME電極を大脳皮質運動野硬膜外に2個植込み，慢性刺激を行った．MRIを用いた画像誘導装置で硬膜上から中心溝を同定し，cortico-spinal MEPのD波をモニターしながら電極の留置方法を検討したところ，足の領域では電極を上矢状静脈洞のすぐ外側で，上矢状静脈洞に平行に電極を留置し，手の領域では中心溝に平行に中心前回後半部に留置することにより，双極刺激で最も高振幅のD波を記録することができた．

### 大脳皮質運動野刺激の効果と刺激条件の決定

刺激条件は，刺激強度3～6 V(運動誘発閾値の80%の強度)，刺激頻度25 Hz，刺激幅0.210 msに統一した．また，術前と刺激開始後1，2，3，6か月の各時点で，運動機能(Fugl-Meyer検査，運動速度など)の変化について検討し，その期間の実際の刺激時間数との比較を行った．実際の刺激時間数については，患者の記録を参考にしながら，外来受診時にimplantable pulse generatorに記録された刺激時間数を確認して，1日の刺激時間数を算出した．

6か月間の大脳皮質運動野の慢性刺激では，6例中3例で上肢のFugl-Meyer scaleが5～8点増加し，運動機能の改善を認めた．また，この3例では1日の刺激時間は2～3時間半であった．一方，1日の刺激時間が9時間と8時間に及んだ2例では逆にFugl-Meyer scaleが著しく減少し，運動障害が増悪したが，Fugl-Meyer scale減少後の早い時期に刺激時間を強制的に制限することで，術前に近いレベルまで回復した．この1日の

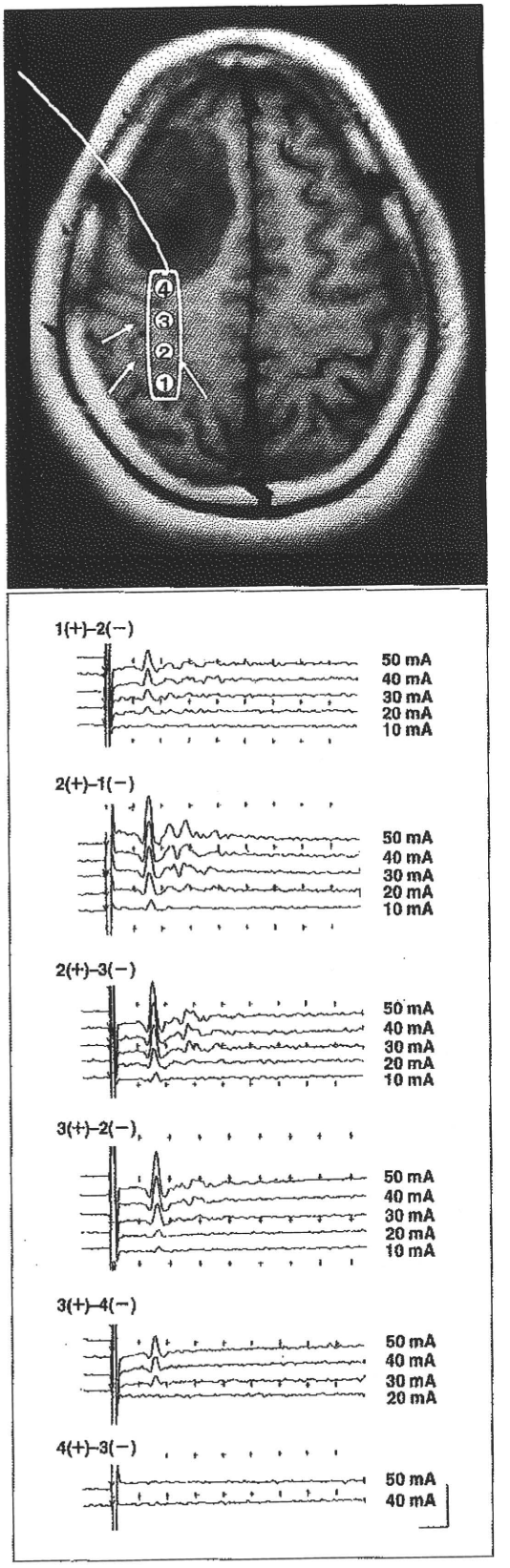


**図 2.**

a：大脳皮質上の多連円盤電極．
矢印は中心溝の位置を示す．

b：隣接する刺激点を用いて双極刺激を行い，D波を比較したもの．
①②③④は，多連円盤電極の刺激点1，2，3，4に一致する．

(文献14より引用)

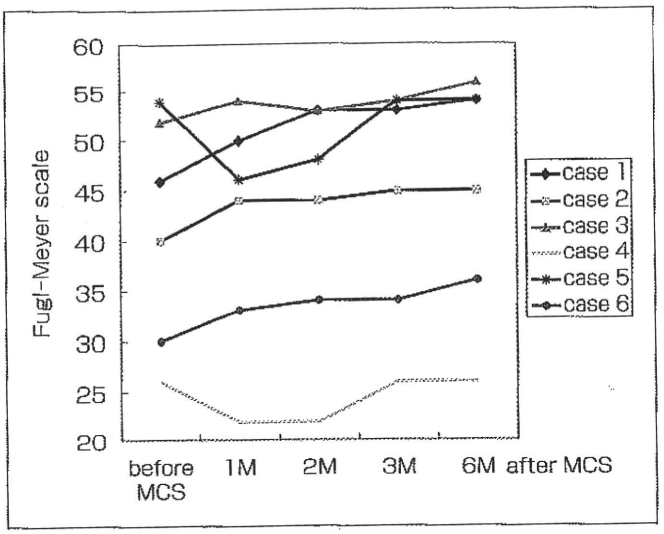


**図 3.** 運動野刺激開始後の上肢の Fugl-Meyer scale の変化
1日の刺激時間が3時間程度の4例(case 1, 2, 3, 6)では Fugl-Meyer scale が改善したが，8時間と9時間であった2例(case 4, 5)では逆に増悪した．この2例の刺激時間を強制的に制限したところ，刺激開始前のレベルまで回復した．

刺激が長時間に及んだ2例では，刺激による除痛が得られたものの，あまり after effect が得られないため，長時間の刺激を避けられなかった症例であった．そこで，刺激装置を continuous mode から cycle mode に変更し，長時間の刺激を行わないようにしたところ，運動機能の回復を認めた(図3)．この2例から明らかなように，VAS の減少率と運動機能の改善には明らかな相関は認めなかった．

## 大脳皮質運動野刺激の要点

大脳皮質運動野刺激の電極留置の方法(図4)としては，① 局所麻酔あるいはプロポフォール麻酔を用いた覚醒下手術によって開頭し，刺激による muscle twitch や muscle contraction を指標とする方法，② グリッド電極によって最適の刺激部位を決定し，2期的に電極留置を行う方法，③ MRI を用いたニューロナビゲーションで中心溝を同定し，中心前回上に電極を留置する方法，④ 運動誘発電位を用いる方法がある．

① では患者が緊張状態にあり，確実な判定が困難であることが少なくない．② では通常のグリッド電極を用いた場合には75%以上の脳表が刺激点でカバーされないため，最適の留置部位を決定するのが困難である(図5)．③ では電極が中心前回の上に留置されるのみで，実際に皮質下の pyramidal tract neuron がどのように刺激されているかを知ることはできない．④ では cortico-spinal MEP を用いる方法と，誘発筋電図を用いる方法がある．cortico-spinal MEP を記録するためには，脊髄硬膜外に記録電極をあらかじめ留置する必要があるが，全身麻酔下でも安定した記録が可能で，最適の刺激部位を決定するための電極

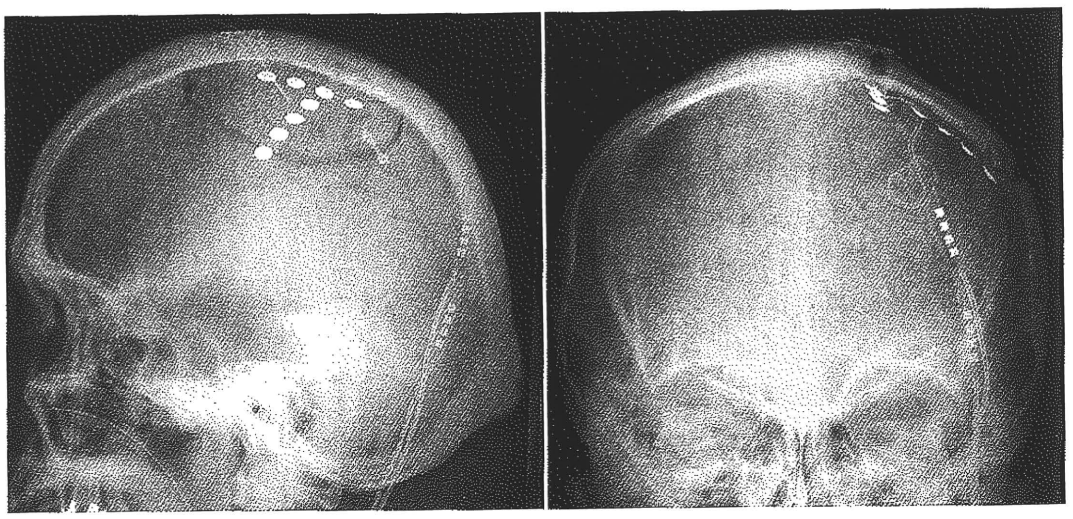

**図 4.** 大脳皮質運動野刺激に用いる刺激電極の留置方法

位置の微量調整も可能である．誘発筋電図を用いる方法では，記録方法は容易であるが，train 刺激を用いるために痙攣の誘発に注意する必要がある．また，麻酔の問題もあり，施設によって得意な方法を用いるのが良いと考える．さらに，現在使用することが可能な慢性植込み型の刺激装置も電極の留置方法で重要なポイントとなる．現在，市販されている慢性の脳刺激装置は，脳深部刺激療法を目的としているため，単極刺激では cathode 刺激に限られ，anode 刺激ができない．大脳皮質刺激では脳表から垂直方向に通電が可能な anode 刺激が有効であるため，双極刺激を選択することになり，電極の留置部位の決定には運動誘発電位のモニタリングが特に有用である．

運動機能回復を目的とした大脳皮質運動野刺激が 2006 年[15]と 2008 年[16]に報告されているが，これらの報告は 3 週あるいは 6 週間のリハビリテーションと同時に大脳皮質運動野刺激を行い，その後に刺激装置を抜去するもので，長期間の慢性刺激についての検討はされていない．今回の研究では，6 か月以上の運動野の慢性刺激で運動機能が改善することが明らかとなった．しかし，刺激条件の設定が重要であり，持続的に長時間の刺激を行うと逆に運動機能を悪化させることが明らかとなった．これらの事実から，運動閾値の 80％の刺激強度を用いた場合には，1 日の刺激を 3 時間程度に制限する必要があると結論された．

## まとめ

大脳皮質運動野刺激は，難治性疼痛，不随意運動の治療に臨床応用され，運動麻痺の治療への臨床応用も期待される．これらの研究は，一次運動野，運動前野，補足運動野，一次知覚野と大脳基底核に錐体路を含めた脳内ネットワークの関連を明らかにするのに有効であり，今後の発展が期待される．

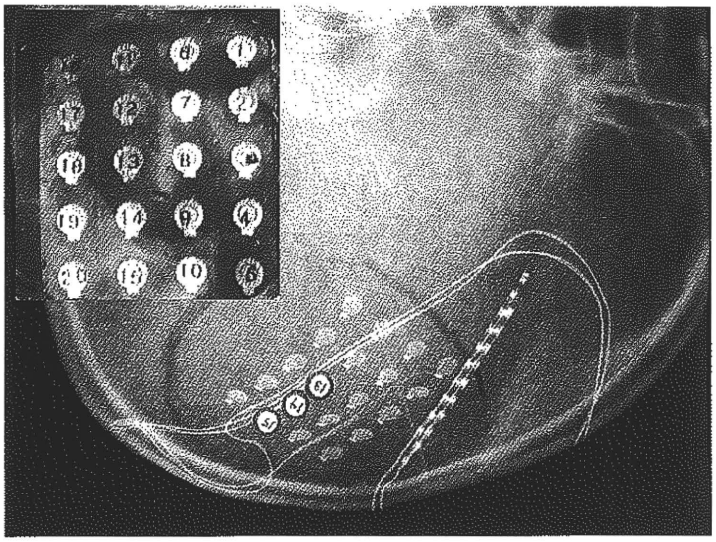

図 5. グリッド電極(左上)と頭蓋内硬膜外腔に留置したもの

## 文　献


1) Yamamoto T, et al : Deep brain stimulation for the treatment of parkinsonian, essential, and poststroke tremor : a suitable stimulation method and changes in effective stimulation intensity. *J Neurosurg*, 101 : 201-209, 2004.
2) Limousin P, et al : Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Eng J Med*, 339 : 1105-1111, 1998.
3) Krauss JK, et al : Bilateral stimulation of globus pallidus internus for treatment of cervical dystonia. *Lancet*, 354 : 837-838, 1999.
4) 山本隆充ほか：神経因性疼痛に対する DBS 治療. 臨床脳波, 50 : 209-215, 2008.
5) Tsubokawa T, et al : Chronic motor cortex stimulation in patients with thalamic pain. *J Neurosurg*, 78 : 393-401, 1993.
6) Yamamoto T, et al : Pharmacological classification of central post-stroke pain : comparison with the results of chronic motor cortex stimulation therapy. *Pain*, 72 : 5-12, 1997.
7) Katayama Y, et al : Poststroke pain control by chronic motor cortex stimulation : neurological characteristics predicting a favorable response. *J Neurosurg*, 89 : 585-591, 1998.
8) Peyron R, et al : Electrical stimulation of precentral cortical area in the treatment of central pain : Electrophysiological and PET study. *Pain*, 62 : 275-286, 1995.
9) Nguyen JP, et al : Treatment of deafferentation pain by chronic stimulation of the motor cortex :

Report of a series of 20 cases. *Acta Neurochir (Wien)*, 68 : 54-60, 1997.
10) Saitoh Y, et al : Motor cortex stimulation for central and peripheral deafferentation pain : Report of eight cases. *J Neurosurg*, 92 : 150-155, 2000.
11) 山本隆充ほか：神経障害性疼痛に対する Dual-lead を用いた脊髄刺激療法と low-dose ketamine 点滴療法の併用効果. *Pain Research*, 24 : 9-15, 2009.
12) Yamamoto T, et al : Recording of corticospinal evoked potential for optimum placement of motor cortex stimulation electrodes in the treatment of post-stroke pain. *Neurol Med Chir (Tokyo)*, 47 : 409-414, 2007.
13) Katayama Y, et al : Cortico-spinal direct response in humans : identification of the motor cortex during intracranial surgery under general anesthesia. *J Neurol Neurosurg Psychiatry*, 51 : 50-59, 1988.
14) Yamamoto T, et al : Intraoperative monitoring of the corticospinal motor evoked potential (D-wave) : Clinical index for postoperative motor function and functional recovery. *Neurol Med Chir (Tokyo)*, 44 : 170-182, 2004.
15) Brown JA, et al : Motor cortex stimulation for the enhancement of recovery from stroke : A prospective, multicenter safety study. *Neurosurgery*, 58 : 464-471, 2006.
16) Levy R, et al : Cortical stimulation for the rehabilitation of patients with hemiplegic stroke : a multicenter feasibility study of safety and efficacy. *J Neurosurg*, 108 : 707-714, 2008.

特　集　「難治性疼痛の診断と最新の治療」

# 神経障害性疼痛の治療：脳脊髄刺激療法と低用量ケタミン点滴療法

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# Cerebrospinal Stimulation and Low-dose Ketamine Drip Infusion Therapy for the Treatment of Neuropathic Pain

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For the treatment of intractable neuropathic pain, drug challenge test is necessary and useful to examine the pharmacological background of the pain in each case. Based on the results of drug challenge test, we can select the candidates for low-dose ketamine drip infusion (LDKDI) therapy and cerebrospinal stimulation therapy. In cerebrospinal stimulation therapy, dual-lead spinal cord stimulation should be selected at first, since we can insert electrodes percutaneously and this is suitable for both the test stimulation and chronic implantation. For the treatment of peripheral deafferentation pain, which includes phantom limb pain and peripheral nerve injury pain, deep brain stimulation therapy of the thalamic relay nucleus is suitable. Motor cortex stimulation therapy is suitable for the treatment of central deafferentation pain, which includes post-stroke pain. LDKDI therapy combined with cerebrospinal stimulation therapy achieves remarkable pain reduction in the treatment of neuropathic pain.

**Key words:** Pain, SCS, DBS, MCS, Drug Challenge Test
痛み，脊髄刺激，脳深部刺激，大脳皮質運動野刺激，ドラッグチャレンジテスト
(J. Nihon Univ. Med. Ass., 2010; 69 (3): 176–182)

## はじめに

外科的に脊髄視床路などの痛覚伝導路を破壊する方法は，主として癌性疼痛など，痛覚伝達系に過剰な信号が送られることによって出現する疼痛，すなわち侵害受容性疼痛の治療に用いられてきた．しかし，経口オピオイド療法の開発や神経ブロック療法の進歩によって，侵害受容性疼痛の治療を目的とした神経伝導路の破壊術の頻度は激減している．一方，Post-stroke pain，幻肢痛，腕神経叢の損傷，各種末梢神経の損傷など，体性感覚系の求心路が損傷を受けた後に二次的に出現する神経障害性疼痛に対しては，経口オピオイドや神経ブロックの効果が不十分であることが多いので，脳脊髄刺激療法が選択されることが多い．

脳脊髄刺激療法には，脊髄刺激療法[1,2]，脳深部刺激療法[3,4]，大脳皮質運動野刺激療法[5~7]などがある．脊髄刺激は経皮的に脊髄硬膜外腔に刺激電極を挿入することが可能で，容易に試験刺激を行うことができるので，テスト刺激を兼ねて第一に選択されることが多い．また疼痛の原因から刺激法を選択すると，幻肢痛や神経根損傷後疼痛など末梢神経の損傷による神経障害性疼痛に対しては視床知覚中継核(視床 Vc 核)の刺激[3,4]が有効で，post-stroke pain など中枢神経の損傷が原因の神経障害性疼痛では，大脳皮質運動野刺激の有効例が多い[5~7]．

手術適応の決定にあたっては，ドラッグチャレンジテスト[6,8]によって痛みの薬理学的背景を明らかにすることが重要であり，ドラッグチャレンジテストで有効な薬物を術後に併用することもできる．本稿では，ドラッグチャレンジテストに基づく疼痛評価の有用性と低用量ケタミン点滴療法を紹介するとともに，脊髄刺激療法，脳深部刺激療法，大脳皮質運動野刺激療法を用いた神経障害性疼痛の治療法について述べる．

## I. ドラッグチャレンジテスト
### (日本大学脳神経外科)

ドラッグチャレンジテスト[6]は，モルフィンテス

ト，サイオペンタールテスト，ケタミンテストの3者を用いている．ケタミンテストは，5分間隔で生食を2回投与後，同様に5分間隔でketamine hydrochlorideを5 mg，合計25 mgまで静脈内投与する．モルフィンテストは，同様に5分間隔でmorphine hydrochloride 3 mgを合計18 mgまで静脈内投与する．また，サイオペンタールテストは，同様に50 mgのthiopental sodiumを5分間隔で合計250 mgまで静脈内投与するが，途中で入眠した場合は，その時点で中止する．Visual Analogue Scale (VAS)を連続的に測定し，(薬物投与後VAS÷薬物投与前のVAS)×100%＝%VASとして，%VASが60%以下となったもの，すなわち薬物投与前と比較して，VASが40%以上減少したものをsensitive例，40%以下のものをresistant例としている．サイオペンタールテストで入眠直前までVASが変化しない症例については，脳脊髄刺激療法の適応外としている．また，morphine-sensitiveな症例については経口オピオイドの投与も考慮する．

Post-stroke painの自発痛に対しては，120例中55例がketamine-sensitiveで，65例がketamine-resistantであった．ketamine-sensitive群とketamine–resistant群で比較を行うと，Table 1のように，不快な異常感覚や精神的な異常感覚を訴えた症例は全例がketamine–resistantな症例であり，めまい感，頭重感，疲労感，嘔気などの軽度な副作用もketamine-resistant群では20%に認められたが，ketamine-sensitive群では僅か5.4%であり，ketamine-sensitiveな症例においては問題とならないものと考えられた[9]．

低用量ケタミン点滴療法は，ドラッグチャレンジテストでketamine-sensitiveな症例に対して，100 mlの生食に20 mgのケタラール®(0.33 mg/Kg)を加え，約1時間かけて点滴する．通常は2週間ごとに外来で点滴投与を行なう．併用薬は塩酸マプロチニン(Ludiomil®) 10～30 mg/day，ブロマゼパム(Lexotan®) 2～6 mg/day，ガバペンチン(GABAPEN®) 600～2400 mg/dayを投与する[10,11]．またmorphine-sensitiveで経口オピオイドを希望した症例にはMSコンチン®30 mg/dayなどを投与する(Table 2)．また，本治療法については，本学の学術・臨床研究審査委員会の承認を得ている．

私どもの120例のpost-stroke painに対するケタミンテストの結果では，自発痛に対して55例(45.8%)がketamine-sensitiveであった．また，自発痛の明らかな改善を認めない症例の中でも，8例ではアロデニアが著しく抑制されていた．これらの結果を総合すると，ケタミンは120例のpost-stroke painの中で，63例(52.5%)に有効であることが確認された．また，自発痛に対してketamine-sensitiveであった55例のケタミンテストの平均値を比較すると，ケタラール20 mgの投与によってVASが平均で70%以上減少し，それ以上の投与量を用いても明らかな変化を認めなかった(Fig. 1)．そこで，低用量ケタミン点滴療法におけるケタラール®の投与量を20 mg (0.33 mg/Kg)に決定した[9]．

**Table 1**　Drug challenge test with ketamine for spontaneous pain

| ketamine | -sensitive | -resistant |
|---|---|---|
| Total caces | 55 | 65 |
| Adverse effects<br>Unpleasant sensation and/or psychological reactions | 0<br>(0%) | 17<br>(26.1%) |
| Dizziness | 2 | 5 |
| Light headache | 0 | 3 |
| Fatigue | 0 | 3 |
| Nausea | 1 | 2 |
| | (5.4%) | (20.0%) |

**Table 2**　Low-dose ketamine drip infusion (LDKI) therapy

(Nihon Univ.)

1. 生食100 ml＋ケタラール20 mg (0.33 mg/kg) 1時間で点滴，2週に1度
2. ルジミオール (Maprotiline p.o. 10–30 mg/day)
3. レキソタン (Bromazepam p.o. 2–6 mg/day)
4. ガバペン (Gabapentin p.o. 600–2400 mg/day)

末梢神経に損傷を有する神経障害性疼痛では，23例中20例(87%)がketamine-sensitiveであり，中枢神経系に損傷を有する神経障害性疼痛に比較して明らかに有効例が多い結果であった．これは，中枢神経系に損傷部位を有する神経障害性疼痛に比較して，末梢神経に損傷部位を有する症例で各種治療の有効率が高い結果と一致している．

ドラッグチャレンジテストによってketamine-sensitiveで，low-dose ketamine点滴療法を施行した55例の検討では，点滴後に明らかに疼痛が抑制される持続時間は3時間から6時間以内が最も多く，24時間以内が69.0%であったが，24時間以上持続するものも31.0%存在した(Fig. 2)．また，長期投与によるケタミン耐性の有無についての検討では，20 mgで開始した26例中，6ヶ月後も20 mgが19例，21～30 mgが5例，10～19 mgが2例で，モルヒネのような耐性は認めなかった事実は，神経障害性疼痛の長期的な治療を行うのに特に有用であると考えられる[9~11]．

ケタミンテストによって情動面の変化を呈する症例が存在したが，低用量ケタミン点滴療法はketamine-sensitiveな症例に行っており，情動の変化のみならず頭痛，嘔気など訴える症例は極僅かであった．また，このような症例でも投与量ならびに投与時間の調整によってコントロールが可能であった．一般にケタラールの副作用が

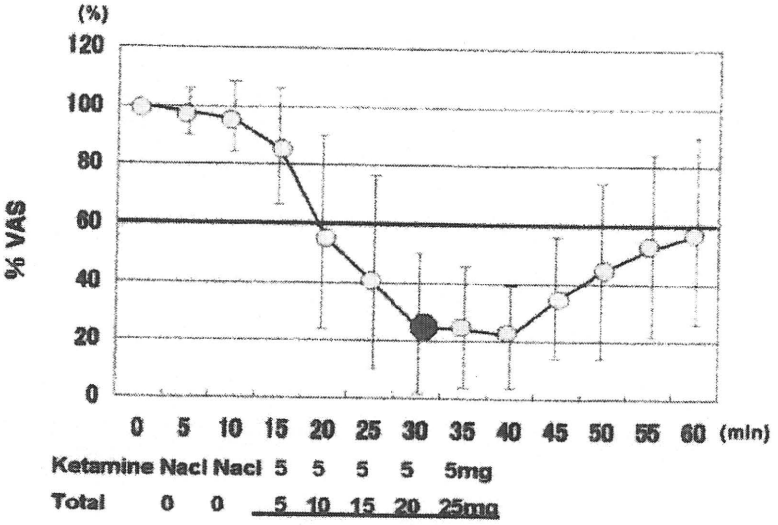


**Fig. 1** ドラッグチャレンジテスト (ケタラール)
%VAS = (薬物投与後の VAS / 薬物投与前の VAS) × 100. 自発痛に対して Ketamine-sensitive 症例 (N = 55) のテストの平均値をプロットしたもの.

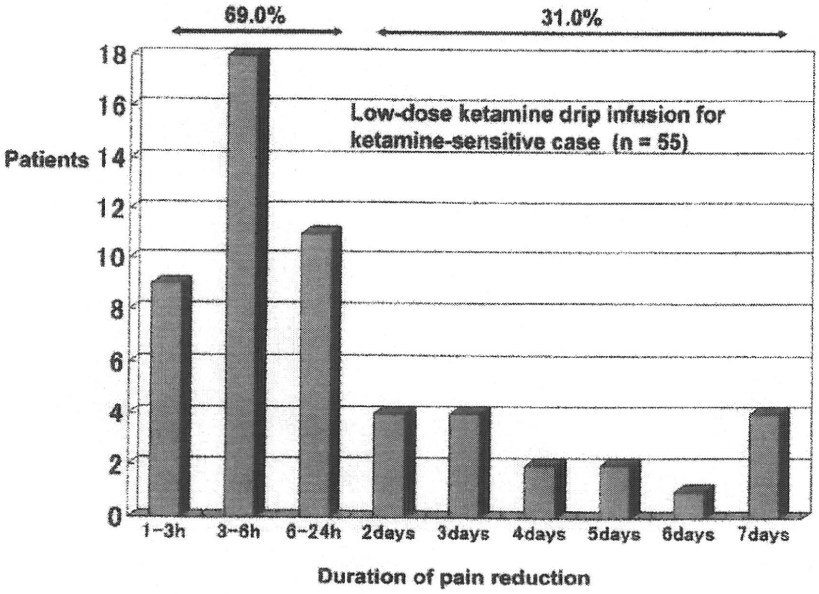


**Fig. 2** Low-dose ketamine 点滴療法による除痛効果の持続時間.

議論されることが多いが，副作用が出現する症例は大多数が ketamine-resistant の症例であり，適切なドラッグチャレンジテストを行うことの必要性を強調したい.

低用量ケタミン点滴療法では，効果の持続時間が短い症例でも一度疼痛を軽減することが疼痛の管理には重要であり，これによって精神的な安定を得られるという症例が多い．また，central sensitization の解除にも有効であると考えられている[12,13]．併用薬として，抗うつ薬，抗不安薬，抗てんかん薬を用いたが，本邦でも使用可能となったガバペンチンには，神経終末からの興奮性アミノ酸の遊離を抑制する作用が報告されており，ケタミンとの相乗効果も期待される[14].

## II. 脊髄刺激療法 (Spinal Cord Stimulation)

脊髄刺激では経皮的に脊髄硬膜外腔に刺激電極を挿入することが可能であるので，容易に試験刺激を行うことができる利点がある．脊髄刺激では，疼痛部に刺激による paresthesia を誘発し，非疼痛部には paresthesia を誘発しないように電極を留置するのが最良の方法である．しかし，脊髄硬膜外に留置した1本の刺激電極を用いる

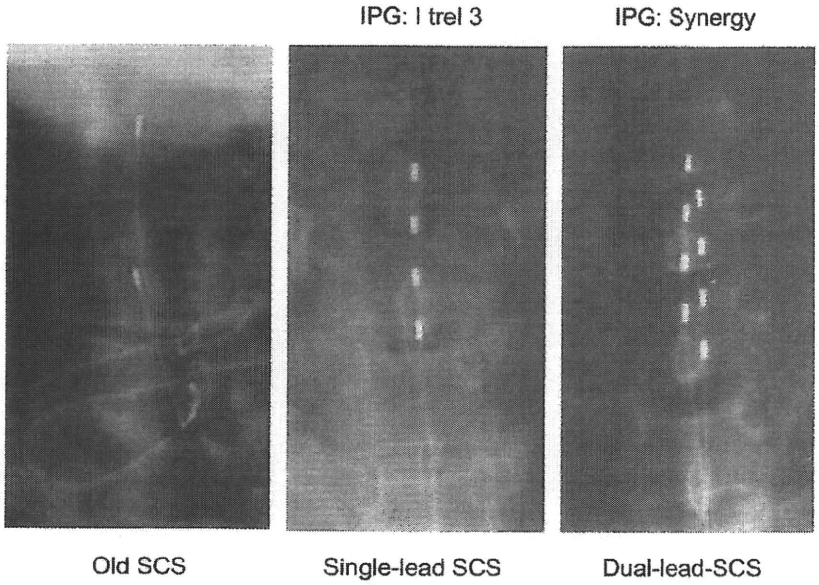


**Fig. 3A**　脊髄刺激法の変遷

**左**：初期の脊髄刺激電極で，刺激点が 1 箇所.
**中**：刺激点が 4 箇所ある脊髄刺激電極.
**右**：刺激点が 4 箇所ある脊髄刺激電極を 2 本脊髄硬膜外に刺入し，1 個の刺激装置に結線する (Dual-lead SCS).

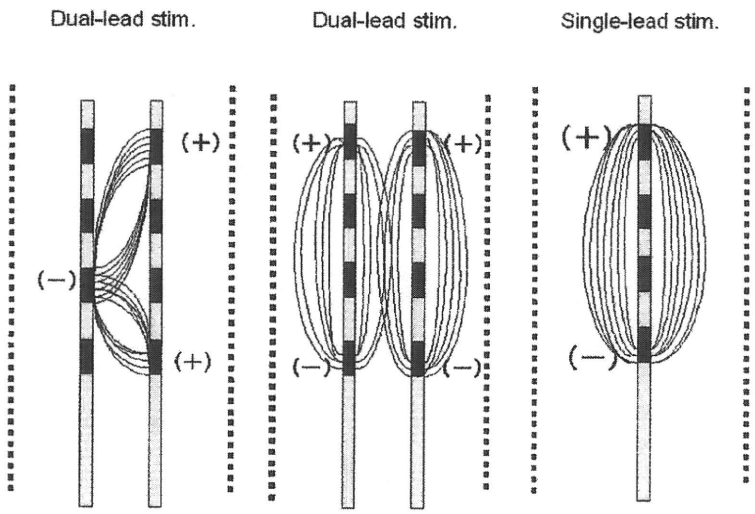


**Fig. 3B**　Dual-lead SCS と Single-lead SCS

Single-lead 刺激と異なり，Dual-lead 刺激では電極間での刺激が可能であり，脊髄に対して横方向の刺激を行うことが出来る．また 2 本の電極を別々に刺激しても電極間の電荷密度を高めることができる.

方法では限界があった．新しく脊髄刺激用に開発されたシナジー刺激装置は，2 本の刺激電極を用いた Dual-lead Spinal Cord Stimulation が可能となり，電極間の刺激あるいは複数の刺激点を選択することによって，疼痛部位に限局した paresthesia を誘発するのが容易となった (Fig. 3).

29 例に対してテスト刺激を行ない，24 例に対して慢性植込みによる Dual-lead SCS を施行した．Dual-lead SCS の効果を VAS の減少率をもとに，Excellent (61–100%の VAS 減少)，Good (31–60%の VAS 減少)，Fair (0–30%の VAS 減少) に分類すると，Post-stroke pain では Excellent が 2 例，Good が 6 例，Fair 4 例，Failed-