reotide treatment in tumor shrinkage, tumor softening, and improvement of the patient's general condition by reducing the serum GH level, which also reduces perioperative morbidity [9–17]. However, whether this treatment improves surgical results in cases of the GH-secreting macroadenoma remains controversial [18, 19]. Recent studies have shown that preoperative octreotide treatment is beneficial in some but not all types of macroadenoma [13, 15]. Although reducing the size of GH-secreting adenoma by octreotide is thought to improve surgical results, the effect of octreotide treatment on tumor volume is unpredictable and is not correlated with its endocrinologic effects [9, 10, 18, 20].

Here, we review our experience with 32 acromegalic patients with GH-secreting macroadenoma who underwent short-term preoperative octreotide treatment (2–3 weeks). We aimed to determine for which types of GH-secreting adenoma, preoperative octreotide treatment is effective, and whether there are predictive factors for tumor shrinkage. This is the first substantial report regarding preoperative octreotide treatment for acromegaly in Asia.

Materials and Methods

Patients

During the period from December 1993 to May 2004, 71 acromegalic patients underwent 82 surgeries (78 transsphenoidal surgeries and 4 craniotomies) at Osaka University Hospital, and 44 of them underwent preoperative treatment with octreotide (Sandostatin). Preoperative octreotide treatment was recommended particularly for patients with GH-secreting macroadenoma, but not for those with microadenoma.

To evaluate the efficacy of short-term octreotide treatment, the following 12 patients were excluded; seven who had undergone long-term octreotide treatment (two who were treated for over a year at other hospitals, and five with a large adenoma that extended into the middle or posterior fossa who were treated for over 5 weeks), four with GH/PRL-secreting adenoma who were also treated with dopamine agonists, and one treated 20 years previously with conventional radiotherapy. Therefore, 32 patients, 18 men and 14 women were included in this study. Mean patient age was 45.6 years, with a range of 22 to 68 years. Thirty cases were newly diagnosed, and two were recurrent. Appropriate written informed consent was obtained from each patient and family prior to therapeutic procedure.

Endocrinologic evaluation

All patients underwent careful endocrinologic examination in the pre- and postoperative periods. Examinations included measurements of the serum GH and IGF-1 levels, TRH test, LH-RH test, insulin stimulation test, and a 75 g-oral glucose tolerance test (OGTT). In addition, octreotide challenge tests, with blood samples taken before and 30 min and 1, 2, 4, 6, and 12 hours after subcutaneous injection of 100 μg octreotide were performed in 30 of the 32 patients. Bromocriptine challenge tests, with blood samples taken before and 1, 2, 4, 8, 12, and 24 hours after oral administration of 2.5 mg bromocriptine (Parodel), were also performed in 29 patients. Serum GH levels and IGF-1 levels were measured by a commercial kit (GH-immunoradiometric assay (IRMA), IGF-1-IRMA, Dai-ichi Radioisotope Laboratory, Tokyo, Japan) [21].

The data are shown as mean ± S.E.M. (range). Reductions in serum GH or IGF-1 levels and tumor volume are shown as percentages of post-/pretreatment values.

Tumor classification based on magnetic resonance images

All patients underwent magnetic resonance (MR) imaging at 1.5 Tesla, which provided 3 mm-thick T1-weighted slices before and after intravenous gadolinium administration. Pituitary macroadenoma was revealed in all patients, irrespective of its size. Referring to the lateral extension in coronal sections, adenomas were classified into five groups according to the Knosp grade: grade 0, normal findings within the cavernous sinus space; grade 1, tumor extending and passing the medial aspect of the intra- and supracavernous internal carotid artery (ICA) but not going beyond the intercarotid line; grade 2, tumor extending beyond the intercrossed line and slightly past the tangent on the lateral aspects of the intra- and supracavernous ICA; grade 3, tumor extending past the lateral tangent of the intra- and supra-cavernous ICA; grade 4, total encasement of the intracavernous carotid artery [22]. Suprasellar extension was observed in nine patients and compression of the optic chiasm was observed in seven.

Preoperative treatment with octreotide

Patients received subcutaneous injections of octreotide at a dose of 100 μg three times daily, the standard dose covered by general health insurance in Japan, until the day before the operation, for 2 weeks in 26 patients and 3 weeks in 6 patients. All patients underwent abdominal echography before or during treatment to screen for gallstones.

Endocrinologic effects of short-term octreotide treatment were evaluated by comparing serum GH and IGF-1 levels on the day of or day before surgery with pretreatment values.

MR images were obtained within 3 days before surgery for 27 patients. The effect of octreotide treatment on tumor volume was estimated by comparing the MR images with those obtained during the pretreatment period. Because each tumor was shaped irregularly with or without invasion into surrounding structures (sphenoid sinus or cavernous sinus), tumor size was estimated by measurement of the maximum width, length, and height on the MR images. Tumor shrinkage was defined as a greater than 2 mm reduction in the maximum diameter [15]. Tumor volume was calculated according to the formula $V = \text{height} \times \text{length} \times \text{width} \times \pi/6$ [10, 14, 23].

To evaluate the effect of octreotide on tumor consistency, intraoperative findings on tumor texture was classified as hard, soft, and fluid-like according to the surgical records.

Postoperative remission criteria and follow up

For postoperative evaluation, we used the remission criteria of nadir GH levels on OGTT less than 1.0 ng/ml, and normal age and sex-related IGF-1 levels [3, 24, 25]. All patients underwent 75 g OGTT in the postoperative period (2–3 weeks after surgery). Serum IGF-1 level sampled at least 3 months after surgery was evaluated. Normal ranges for IGF-1 were as follows (ng/ml): 20–29 years, male 85–369, female, 119–389; 30–39 years, male 67–318, female 73–311; 40–49 years, male 41–272, female 46–282; 50–59 years: male 59–215, female 37–266; 60–69 years, male 42–250, female 37–150; 70– years: male 75–218, female 38–207 (−1.96 S.D.– + 1.96 S.D., Dai-ichi Radioisotope Laboratory, Tokyo, Japan)

Results

Effects of short-term octreotide treatment on GH and IGF-1 levels

The pretreatment serum GH level was 82.8 ± 22.2 ng/ml (range 9–436 ng/ml) and that of IGF-1 was 1055 ± 53.4 ng/ml (385–1480 ng/ml). In all patients, the serum GH level was not decreased below 1 ng/ml during the 75 g OGTT. Endocrinologic effects of short-term octreotide treatment are shown in Table 1. Serum GH levels were reduced to 22.2 ± 4.4 ng/ml (0.5–88.8 ng/ml, $P<0.01$, paired t-test), corresponding to a mean reduction to 31.9 ± 6.9% (1.9–118.9%) of the pretreatment value. Serum IGF-1 levels were reduced to 553 ± 42.0 ng/ml (147–866 ng/ml, $P<0.001$, paired t-test), corresponding to 51.6 ± 3.2% (22.4–77.8%) of the pretreatment value. Serum GH levels were reduced below 2.5 ng/ml in 6 of 32 patients (18.8%), and IGF-1 was decreased to the normal range in 4 patients (12.5%).

Effects of octreotide treatment on tumor volume and Knosp classification

Mean tumor diameter before octreotide treatment was 20.6 ± 0.9 mm. Tumor shrinkage was observed in 14 of 27 patients (51.9%) who underwent preoperative MR imaging. In patients in whom tumor shrinkage was observed, the mean diameter reduction was 2.8 ± 0.4 mm, corresponding to a volume reduction to 68 ± 2% of the initial volume. Subsequent to tumor shrinkage, the tumors in 4 patients were reclassified to other Knosp grades; 2 patients from grade 1 to grade 0 (Fig. 1) and 2 from grade 2 to grade 1. Compression of optic chiasm disappeared in 2 of the 7 patients. Of 10

Table 1. Effect of short-term preoperative octreotide treatment

Serum GH level (pre-Oct; ng/ml)	82.8 ± 16.4
Serum GH level (post-Oct; ng/ml)	22.2 ± 4.4
Ratio of serum GH levels (post/pre-Oct; %)	31.9 ± 5.4
Serum IGF-1 level (pre-Oct; ng/ml)	1055 ± 53.4
Serum IGF-1 levels (post Oct; ng/ml)	553 ± 42.0
Ratio of serum IGF levels (post/pre-Oct; %)	51.6 ± 3.2%
Occurrence of tumor shrinkage	52% (14/27 patients)
Volume reduction (post/pre,%) (in patients with tumor shrinkage)	68 ± 2%

Oct: octreotide treatment, mean ± S.E.M are shown.

Fig. 1 Representative coronal T1-weighted MR image with gadolinium enhancement (*left*: pre-, *right*: post-octreotide treatment) shows tumor shrinkage in a 44-year-old male acromegalic patient. With volume reduction in width as well as in height, the tumor was reclassified from Knosp grade 1 to grade 0.

patients with prominent reduction in the serum GH level (to less than 10% of the pretreatment value) after octreotide treatment, 8 showed tumor shrinkage. However, in total, there was no significant difference in octreotide-induced reduction in the GH level between the group with tumor shrinkage and the group without shrinkage (P = 0.13, Mann-Whitney U-test).

Based on MR images before octreotide treatment, patients were classified into five groups according to the Knosp classification: grade 0 (n = 5), grade 1 (n = 9), grade 2 (n = 6), grade 3 (n = 7), grade 4 (n = 5). The effect of octreotide treatment and surgical results differed between these groups (Table 2). When these groups were combined into two larger groups (grade 0–2 and grade 3–4), reduction of serum GH levels by octreotide treatment was significant in the grade 0–2 group compared to the grade 3–4 group (mean reduction to 27.0% versus 52.9%, P<0.05; Mann-Whitney U-test). Tumor shrinkage was also observed more frequently in grade 0-2 groups (62.5%) than in grade 3–4 groups (36.4%).

Postoperative endocrinologic remission was observed in 16 (50%) of 32 patients. With respect to initial Knosp grade, surgical remission was observed in 100% of the patients with a grade 0 tumor, 78% of the patients with grade 1 tumor, 50% of the patients with a grade 2 tumor, 14% of the patients with a grade 3 tumor, and 0% in the patients with a grade 4 tumor (Table 2).

Octreotide and bromocriptine challenge tests

Before octreotide treatment, 30 patients underwent an octreotide challenge test. Subcutaneous injection of 100 μg octreotide reduced the mean serum GH level from 78.1 ± 19.4 ng/ml (10.4–567 ng/ml) to 10.4 ± 4.7 ng/ml (0.8–140.7 ng/ml), corresponding to a mean reduction to 16.1 ± 3.4% (1.9–92.7%) of the baseline value. There was a rough correlation in reduction of the serum GH level between results of the octreotide challenge test and short-term preoperative octreotide treatment ($r = 0.42$, $r^2 = 0.17$, $P<0.05$). A poor response in the octreotide challenge test indicated poor response to preoperative octreotide treatment.

With respect to Knosp classification, a significant difference in GH reduction in response to the octreotide challenge test was observed between the grade 0–2 group and grade 3–4 group. Mean reductions in serum GH levels were to 10.6% and to 29.6% of baseline values, respectively (P<0.05, Mann-Whitney U-test). Twenty-five patients underwent both the octreotide challenge test and post-octreotide MR imaging. The reduction of GH level in response to octreotide challenge test was to 9.6 ± 2.6% of the baseline value in patients with tumor shrinkage, significantly lower than the reduction to 26.8 ± 7.0% of the baseline value in patients without tumor shrinkage (P<0.01, Mann-Whitney U-test). However, when a good response to the octreotide challenge test was defined as reduction

Table 2. Octreotide effect and surgical results relative to Knosp classification

Knosp grade	n	Post/pre-Oct (%)				Surgical remission	
		GH	IGF-1	Mean tumor diameter (mm)	Shrinkage occurrence	n	Rate
Grade 0	5	28.1	62.3	15.5	33% (1/3)	5	100%
Grade 1	9	22.2	52.9	15.8	72% (5/7)	7	78%
Grade 2	6	23.9	75.5	19.2	67% (4/6)	3	50%
Grade 3	7	49.6	45.4	22.0	29% (2/7)	1	14%
Grade 4	5	50.2	46.9	26.0	50% (2/4)	0	0%
Total	32	31.9	51.6	20.6	52% (14/27)	16	50%

Oct: octreotide treatment

in the serum GH level to less than 10% of the pretreatment value or 2.5 ng/ml, there was no correlation between good response and the occurrence of tumor shrinkage (P = 0.07, χ^2 test with Fisher's exact probability method) (Table 3).

Bromocriptine suppressed serum GH level from 72.7 ± 16.2 ng/ml (9.1–466.2 ng/ml) to 25.6 ± 10.1 ng/ml (0.6–304.5 ng/ml), corresponding to the reduction to 34.4 ± 6.3%. The difference between the mean reduction of the serum GH levels of 28.8 ± 4.8% in the grade 0–2 group and of 45.8 ± 15.0% in the grade 3–4 group was not significant (P = 0.64, Mann-Whitney's U test). Twenty-five patients underwent both the bromocriptine challenge test and postoctreotide MR imaging. Reduction in the serum GH level in response to bromocriptine challenge test was 29.9 ± 6.9% in patients with tumor shrinkage, and to 46.7 ± 13.1% of baseline values in patients without tumor shrinkage (no significant difference, P = 0.31, Mann-Whitney U-test). When a good response to the bromocriptine challenge test was defined as a reduction to less than 20% of the pretreatment value or 5 ng/ml, there was no correlation between a good response to the bromocriptine challenge test and occurrence of tumor shrinkage (P = 0.29, χ^2 test with Fisher's exact probability method) (Table 3).

Both octreotide and bromocriptine challenge tests and postoctreotide MR imaging were performed for 24 patients. Although a good response to either challenge test alone did not correlate with the occurrence of tumor shrinkage, there was a significant correlation between a good response to both tests and occurrence of tumor shrinkage (Table 3) (p<0.01, χ^2 test with Fisher's exact probability method).

Table 3. Octreotide/bromocriptine challenge test results in relation to the effect of short-term octreotide treatment

	Effect of octreotide on tumor volume		
	Shrinkage	No shrinkage	
Octreotide challenge test (n = 25)			
Good response	10	4	
Other	3	8	NS
Bromocriptine challenge test (n = 25)			
Good response	7	3	
Other	6	9	NS
Octreotide and bromocriptine tests (n = 24)			
Good response in both	7	0	
Other	6	11	P<0.01

χ^2 test with Fisher's exact probability method
NS: not significant

Adverse effects of preoperative octreotide treatment

Tinnitus and transient abdominal symptoms, including abdominal pain, diarrhea, and nausea were observed in more than half of the patients following preoperative octreotide treatment and resolved within 3–5 days. There were no major complications during the 2–3 weeks of octreotide treatment.

Surgical finding on tumor texture

According to surgical records, tumor texture was classified as hard in five patients, soft in 21, and fluid-like in six. Four tumors which had partly hard portions were classified as hard. After octreotide treatment, no tumor showed fibrous change. All of the six patients with fluid-like tumors were the good responders in both octreotide and bromocriptine tests.

Discussion

Compared to the currently available long-acting form of octreotide (octreotide-LAR) [26], octreotide which requires daily injection is more suitable for short-term treatment. Our results indicated that short-term preoperative octreotide treatment had a beneficial effect in acromegalic patients who showed good GH responses to both octreotide and bromocriptine challenge tests and those with adenoma of Knosp grade 1 or 2.

The effect of short-term preoperative octreotide treatment in our study (Table 1) was consistent with that of previous studies that used the same dose and treatment period [13, 20]. Other studies have shown a more profound reduction in serum GH and IGF-1 levels with higher doses and longer treatment periods [10, 13, 15, 18, 26, 28]. Dose and treatment period should be modified when the objective of preoperative treatment is to lower the serum GH level and to improve the patient's general condition [29]. However, we have rarely seen patients with severe cardiac or respiratory problems in response to general anesthesia or transsphenoidal surgery. Although there were no major cardiac or respiratory complications in our series of patients, we cannot conclude that preoperative octreotide treatment decreased the surgical morbidity.

From a surgical aspect, the most anticipated effect of preoperative octreotide treatment is reduction of tumor volume and tumor softening. Tumor shrinkage was observed in 52% of our patients with a mean reduction to 68% of the initial volume. Similar to the results of Lucas-Morante *et al.*, tumor shrinkage occurred within 2 weeks of a daily dose of 300 μg octreotide [20], thus a treatment period of 2–3 weeks appears to be sufficient for patients who are responsive to octreotide.

The effect of reducing the tumor to 68% of pretreatment volume would be negligible for large adenomas of Knosp grade 3 or 4 with a high likelihood of invasion into the cavernous sinus. Even in a good responder, it is unlikely that octreotide treatment could transform an invasive adenoma into an enclosed adenoma [13, 15]. For adenomas classified as Knosp grade 0, a high remission rate can be obtained by surgery alone, and there appears to be no additional benefit. However, for Knosp grade 1 and 2 adenomas, reduction of the tumor volume would be beneficial and aid in total surgical removal. As indicated in other reports [13, 15], preoperative octreotide treatment is beneficial for improving the surgical remission rate in cases of enclosed adenomas with no apparent or suspected invasion, *i.e.*, Knosp grade 1 and 2 adenomas. Our results also indicate that the endocrinologic effect of octreotide treatment is more profound in Knosp grade 0–2 tumors than in Knosp grade 3–4 tumors.

Previous studies have indicated that octreotide treatment induces various degrees of tumor shrinkage in 23–60% of patients using different criteria for tumor shrinkage as well as different doses and treatment periods [9–17]. However, octreotide-induced tumor shrinkage is unpredictable, and does not correlate with the endocrinologic effect [9, 10, 18, 20]. It should be mentioned that very poor endocrinologic response appears to be a negative indicator of tumor shrinkage. Somatostatin receptor subtypes 2 and 5 are the predominant receptors found on the surface of pituitary somatotropes [31]. GH-secreting adenomas may express these receptors at an increased density; however, the expression is also highly variable, even within the same tumor, leading to resistance of some tumors to octreotide treatment [31–34]. Somatostatin receptor scintigraphy was unable to predict the effect of octreotide on tumor shrinkage or on hormone response, indicating that factors other than the expression levels of somatostatin receptors are involved in the clinical response to octreotide [34, 35].

Interestingly, our results showed that good responders to both octreotide and bromocriptine challenge tests showed a significantly higher incidence of tumor shrinkage in response to preoperative octreotide treatment (Table 2). This indicates that dopamine D2 receptor is associated with the effect of somatostatin on tumor volume. Some reports have shown that good octreotide responders are more likely to respond to bromocriptine treatment [36, 37], but a relation with tumor shrinkage has not been documented. Rocheville *et al.* reported that the dopamine D2 receptor and somatostatin receptor interact physically through hetero-oligomerization to create a novel receptor with enhanced functional activity [38]. In animal models, interaction between the somatostatinergic and dopaminergic systems have been observed in the basal ganglia and cerebral cortex [39–41]. We suspected that in GH-secreting adenomas, the presence of D2 receptors enhances the effect of octreotide through the interaction, leading to tumor shrinkage and tumor softening. All of the six patients with fluid-like tumors were the good responders in both octreotide and bromocriptine tests in this study. This finding seems to be noteworthy and similar to a previous report [15], although the tumor texture is generally soft in GH-secreting adenomas.

A somatostatin/dopamine chimeric ligand has been developed as a novel tool for treatment of acromegaly [42]. This chimeric ligand may constitute a potent drug for volume reduction of GH-secreting adenomas. It has also been reported that cotreatment with somatostatin and dopamine agonists reduces the serum GH level in patients with acromegaly more effectively than either agonist alone [42, 43], but there has been no evidence regarding reduction tumor volume.

The greatest benefit of surgery for GH-secreting adenomas is the possibility of cure. For large macroadenoma as Knosp grade 3 and 4, the objective of surgery is not to cure but to control the serum GH levels with the combination of other modalities [44]. Long-term octreotide-LAR treatment has shown profound endocrinologic effect and tumor volume reduction and may be useful in the preoperative treatment of large macroadenomas [26]. Of course, short-term octreotide treatment may have less advantage over long-term octreotide-LAR treatment. However, from our results, preoperative octreotide treatment even for short term may achieve better surgical results in Knosp grade 1–2 tumor and good responders in octreotide and bromocriptine challenge tests.

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Stimulation of primary motor cortex for intractable deafferentation pain

Y. Saitoh and T. Yoshimine

Department of Neurosurgery, Osaka University Graduate School of Medicine, Yamadaoka, Suita, Osaka, Japan

Summary

The stimulation of the primary motor cortex (M1) has proved to be an effective treatment for intractable deafferentation pain. This treatment started in 1990, and twenty-eight studies involving 271 patients have been reported so far. The patients who have been operated on were suffering from post-stroke pain (59%), trigeminal neuropathic pain, brachial plexus injury, spinal cord injury, peripheral nerve injury and phantom limb pain. The method of stimulation was: a) epidural, b) subdural, and c) within the central sulcus. Overall, considering the difficulty in treating central neuropathic pain, trigeminal neuropathic pain and certain types of refractory peripheral pain, the electrical stimulation of M1 is a very promising technique; nearly 60% of the treated patients are improved with a higher than 50% pain relief after several months of follow-up and sometimes of a few years in most reports. The mechanism of pain relief by the electrical stimulation of M1 has been under investigation. Recently, repetitive transcranial magnetic stimulation (rTMS) of M1 has been reported to be effective on deafferentation pain. In the future, rTMS may take over from electrical stimulation as a treatment for deafferentation pain.

Keywords: Neuromodulation; motor cortex stimulation; primary motor cortex; repetitive transcranial magnetic stimulation (rTMS); deafferentation pain; navigation.

Introduction

Deafferentation pain is one of the most difficult types of pain to treat and is usually refractory to medical treatment. In 1990, Tsubokawa *et al.* found that pain can be reduced by motor cortex stimulation (MCS) in patients suffering from post-stroke pain [39]. In 1993, pain due to trigeminal peripheral lesion was successfully treated with MCS [18]. Phantom limb pain and brachial plexus injuries also responded to MCS well. Other studies have shown that MCS can provide pain relief in 50–75% of patients with deafferentation pain [14, 18, 20, 31].

Twenty-eight studies involving 271 patients have been reported from Japan ($n = 112$) [12, 13, 32, 39], France ($n = 97$) [17, 20, 24, 36], Belgium ($n = 19$) [8, 25], USA ($n = 11$) [7, 10], Sweden ($n = 10$) [18], U.K. ($n = 10$) [2], Germany ($n = 9$) [4, 27, 28], and Italy ($n = 3$) [1, 5]. This selection includes only original publications with new cases to avoid duplicate publications made on the same patients. All these trials followed an open methodology and no controlled double blind study has been performed so far. Several indications have been studied including most neuropathic pains, but one is clearly far ahead from all others, this of post-stroke pain (59% of all published cases) followed by trigeminal neuropathic pain (17%). All other indications represent less than 10% each. The two exceptions are combinations of central pain and movement disorders. Both publications report a surprising improvement of movement disorders related to MCS, which was initially intended to treat only severe pain [21].

Recently, repetitive transcranial magnetic stimulation (rTMS) has been applied in the treatment of neuropathic pain. The area of stimulation was the primary motor cortex.

Motor cortex stimulation (MCS)

Pharmacological tests (drug challenge tests: DCT)

To clarify pathophysiological mechanisms and to allow patient choice, pharmacological tests, or drug challenge tests (DCT) have been done in two institutes. One study included 39 central post-stroke pain patients who had intractable hemibody pain with dysesthesias. The correlation between the response to pharmacological treatment and the effect of MCS therapy was examined. Yamamoto *et al.* reported that thiopental- and ketamine-responsive and morphine-resistant patients displayed long-lasting pain reduction after long-term use of MCS.

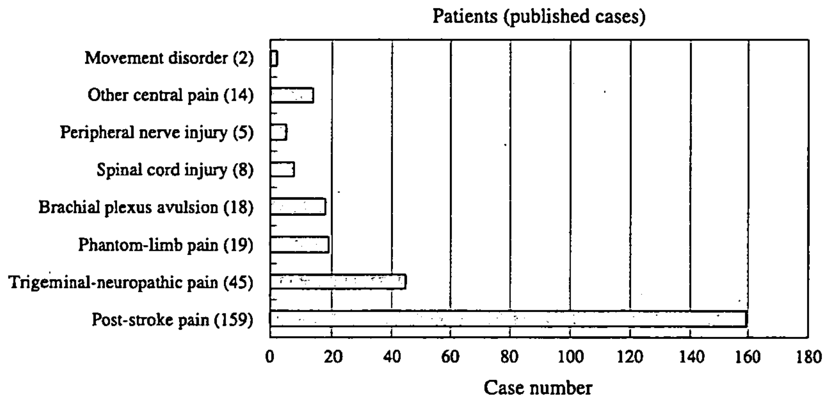

Fig. 1. 67% central pain and 32% peripheral pain. The two exceptions are combinations of central pain and movement disorders (listed here as movement disorders)

Their DCT showed that definite pain reduction occurred in 20% by the morphine test, 56% by the thiopental test, and 48% by the ketamine test. On the basis of these DCT's assessments, it was concluded that there was no obvious difference between thalamic ($n = 25$) and suprathalamic pain ($n = 14$) [41]. Saitoh *et al.* performed DCT including thiopental, ketamine, phentolamine, lidocaine, morphine, and placebo in 18 cases. Of 18 cases in DCT, eight cases scoring "excellent" or "good" pain relief using the MCS were found to have sensitivities to morphine ($n = 5$), ketamine ($n = 4$), thiopental ($n = 4$) or lidocaine ($n = 3$). The other 10 cases scoring "fair" or "poor" pain relief had morphine ($n = 4$) or thiopental ($n = 2$) sensitivities. No relationship was found between morphine sensitivity and pain relief following MCS, and none of the patients was found to be sensitive to phentolamine. Several of the excellent MCS responders had not responded to any drug. The investigators concluded that ketamine might be a useful drug for patient selection [32].

Patients

The most common type is post-stroke pain, which is also the most difficult to treat. All cases, except two, had a severe neuropathic pain history, 67% central and 32% peripheral deafferentation pain. The two exceptions were combinations of central pain and movement disorders. The other reported cases included brachial plexus injury, spinal cord injury, trigeminal neuropathic pain, peripheral nerve injury, and phantom limb pain (Fig. 1).

Surgical methods

Previous reports have described the implantation of epidural electrodes over the precentral gyrus [1, 3, 4, 8, 9, 10, 18, 20, 22, 23]. A small craniotomy, 3–4 cm in diameter, was performed around the central sulcus and an electrode array with four-plate electrodes (diameter 5 mm, model 358; Medtronic Inc., Minneapolis, MN, USA) was inserted in the epidural space. The best location and orientation of the electrode array were, therefore, determined in such a way that bipolar stimulation was offered with an appropriate pair of electrodes. Tsubokawa reported no polarity-related differences in pain relief for most patients [39]. Nguyen *et al.* reported the use of navigation for performing the craniotomy and electrode implantation in the epidural space. The center of the flap should correspond to the target as determined by imaging. Sensory evoked potential (SEP) are recorded from the grid electrode applied on the dura mater. The exact site where the four-plate electrode should be placed depends on the results from the electrophysiological study. They placed the electrode perpendicular to the central sulcus in a parietal-to-frontal lobe direction [22]. Such an epidural approach might not provide optimal pain relief since both the method and the area of test stimulation were restricted by a brief operative period under local anesthesia. Saitoh *et al.* reported that the subdural implant or implant within the central sulcus seemed to be more effective than the epidural implant, because this application make it possible to stimulate M1 more directly. A 20-grid electrode (4×5 array; 0.3 cm electrode diameter; 0.7 cm separation; Unique Medical Co., Tokyo, Japan) was placed subdurally to confirm the locations of the central sulcus by the SEP measurement. For hand or face pain in selected patients, 4-plate electrode was implanted within the central sulcus, and for foot pain, in the interhemispheric fissure in addition of the grid electrode. After implantation of the test electrodes, electrical stimuli were delivered to various areas. Final Resume (Medtronic, Inc., Minneapolis, MN) was implanted after the definition of the best location for pain relief [31, 32].

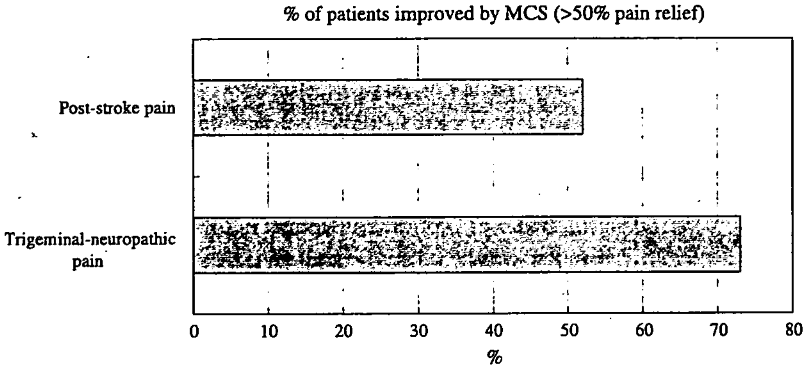

Fig. 2. Post-stroke pain and trigeminal neuropathic pain are the only indications with significant improvement; these two conditions can be considered as valid indications for MCS. 82 of 159 (52%) of post-stroke pain patients showed pain relief (>50%), and 33 of 45 (73%) of trigeminal neuropathic pain patients also did show improvement

Results of motor cortex stimulation

If one considers the difficulty in treating central neuropathic pain, trigeminal neuropathic pain and certain types of refractory peripheral pain, MCS appears to be a very promising technique with nearly 60% of the patients being improved with a higher than 50% pain relief after several months of follow-up and sometimes of a few years in most reports. Considering the number of cases published and their outcome, post-stroke pain and trigeminal neuropathic pain are the only conditions with significant improvement and, hence, these can be considered as valid indications for MCS (Fig. 2).

The relatively big number of patients with post-stroke pain who have been treated by MCS can be explained by two factors: a) post-stroke pain is the biggest patients category with deafferentation pain, and b) the therapeutic options for this condition are very limited. The numbers are smaller in trigeminal neuropathic pain but the results are excellent and very consistent in most reports with more than 70% of the patients being good responders [4, 8, 18, 21, 22]. Other types of central pain and traumatic spinal cord injury have responded with promising results but more studies are needed in order to assess more precisely the efficacy of MCS (Fig. 3). Brachial plexus avulsion pain does not seem to respond well (less than 50% of responders) [7, 22, 32, 36]; results for phantom pain [2, 29, 30, 32] are better but they tend to vary from one report to the other, and the treated cases are few to draw any conclusions. In peripheral nerve injury where spinal cord stimulation (SCS) usually fails, the results of MCS are excellent [2, 18]. If these excellent results were confirmed, the therapeutic strategy of selecting between SCS and MCS should be reconsidered. More studies with rigorous methodology are needed to validate the indications. rTMS trials have a potential in predicting the effectiveness of MCS in the treatment of deafferentation pain [16, 19, 34]. Usually intermittent MCS stimulations were performed. The pain relief induced by MCS was temporary. The longest MCS effect was 24 hours after 30 minutes of stimulation. Some patients had pain relief for only one hour after stimulation. In general, the obtained pain relief by MCS was 3–5 hours [31]. In some cases we observed a decrease of the MCS effectiveness after implantation; however, the cause of this decrease in efficacy has remained unknown. The stimulation parameters were usually as follows: a) relatively low frequency (25–50 Hz), b) impedance between 900 and 1500 ohm, and c) amplitude subthreshold of this that induces muscle twitch.

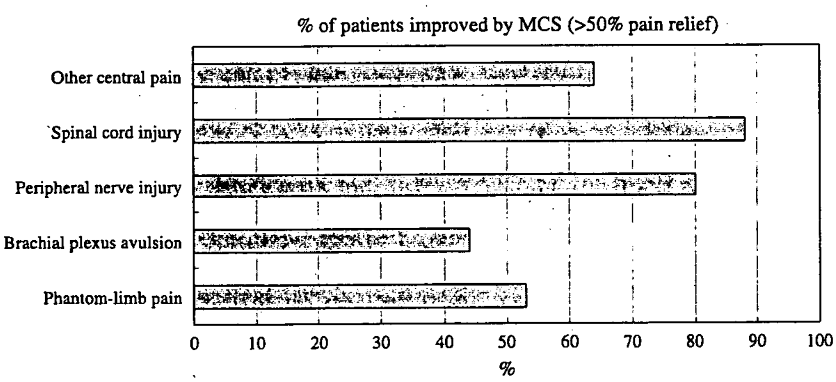

Fig. 3. Other types of central pain and traumatic spinal cord injury have provided promising responses. 10 of 19 (53%) of phantom-limb pain patients showed pain relief (>50%); 8 of 18 (44%) of brachial plexus avulsion; 4 of 5 (80%) of peripheral nerve injury; 7 of 8 (88%) of spinal cord injury; and 9 of 14 (64%) of other types of central pain

Complications

Epileptic seizures have been reported during test stimulation; this was probably due to the variability of test conditions. Paresthesia, dysesthesia and chronic contraction during test stimulation are more common. Speech disorders have also been observed but rarely. The low rate of epileptic seizures during chronic stimulation (0.7%) means that stimulation of the motor cortex with the correct range of parameters is reasonably safe. Paresthesia and dysesthesia have been documented in a small percentage (2.2%) of the published cases. In total, 11.4% of the published cases were associated with an adverse effect. The most serious complications were epi- or subdural hematoma, epileptic seizures, and aphasia or dysphasia and represented 3.6% of the reported cases. The larger craniotomy should decrease the risk of epi- or subdural hematoma and their consequences; a larger craniotomy allows better visual control of the lead, makes less likely the removal of grid or lead, and reduces the resk of inadvertent opening of the dura [20, 31, 32]. The risk of peri-operative hemorrhage is lower compared to DBS.

In one study, two major adverse effects occurred during a long follow-up [32]. Two patients developed cerebral hemorrhage; one died and the other remained in a vegetative state. None of these major complications can be linked to the MCS procedure itself or the chronic stimulation, but they are more closely related to the medical history of the patients. This is especially true in patients with post-stroke pain. It has already been demonstrated than stroke patients are likely to develop a second stoke in the years that follow the first stroke.

Pain relief mechanism with MCS

Tsubokawa *et al.* proposed that in patients with central deafferentation pain, activation of hypothetical sensory neurons by MCS might inhibit deafferentation nociceptive neurons within the cortex [39]. The mechanism of phantom-limb pain is unknown; however, both hyperactivity of peripheral nerves and sensitization of spinal neurons may play a part [3, 38].

So far, positron emission tomography (PET) studies, using ^{15}O-labeled water, have shown no significant rCBF change in the right primary sensory cortex and the primary motor cortex close to the location of MCS [23, 33]. Therefore, it was speculated that MCS does not reduce pain by stimulating either of these cortices directly. Tsubokawa's hypothesis is that MCS activates non-nociceptive fourth-order sensory neurons, which in turn inhibit hyperactive nociceptive neurons in the sensory cortex [39]. However, no significant changes were induced in the parietal cortex, thus indicating that the sensory cortex is probably not the key structure in MCS-induced pain reduction. A model of MCS action was proposed by Garcia-Larrea *et al.* whereby activation of thalamic nuclei directly connected with motor and premotor cortices would entail a cascade of synaptic events in pain-related structures receiving afferents from these nuclei, including the medial thalamus, anterior cingulate and upper brainstem. MCS could influence the affective-emotional component of chronic pain by cingulate-orbitofrontal activation, and lead to descending inhibition of pain impulses by activation of the brainstem; this is also suggested by the attenuation of spinal flexion reflexes [6]. Ipsilateral thalamic hypometabolism has been reported in cases of central pain. Increased rCBF demonstrated by PET indicates increased synaptic activity, which can subserve either excitatory or inhibitory mechanisms. Thalamic CBF changes may reflect the activation of inhibitory processes; this is in agreement with animal studies showing that pathologically hyperactive thalamic neurons are inhibited by MCS [11]. The mechanism of deafferentation pain and that of MCS efficacy have been under investigation, and will probably be better understood in the near future.

rTMS

Recently, rTMS has been applied as a treatment for psychiatric and neuro-degenerative diseases such as depression [15], dystonia [35], schizophrenia, Parkinson's disease, and epileptic seizures [40]. Based on the experience with MCS, rTMS is now beginning to be applied in cases of intractable deafferentation pain [16, 26]. Hirayama *et al.* [9] applied rTMS precisely to primary motor cortex using navigation-guided figure-of-eight coil. Effective treatment was defined as a VAS improvement of more than 30%. Ten of 20 patients (50%) showed significant reductions in pain on the VAS following the stimulation of primary motor cortex. Five Hertz stimulation of M1 was able to reduce intractable deafferentation pain in approximately one every two patients. The pain reduction continued to be significant for three hours. Lefaucheur *et al.* [16] reported that 10 Hz rTMS of motor cortex resulted in a significant but transient relief of chronic pain; this was influenced by pain origin and pain site. The factors most favorable for rTMS treatment are a trigeminal nerve lesion and the presence of sensation in the painful zone. The factors least favorable are brainstem stroke, limb pain, and severe sensory loss. A few other reports have also supported the effectiveness of rTMS on pain [37]. rTMS may be a good predictor of MCS efficacy; Saitoh *et al.* suggested that MCS can be recommended to patients who had good results following rTMS [34]. In the future, it is possible that rTMS could take over from MCS as a treatment for deafferentation pain.

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Correspondence: Youichi Saitoh, Department of Neurosurgery, Osaka University Graduate School, 2-2 Yamadaoka, Suita-shi, Osaka 565-0871, Japan. e-mail: neurosaitoh@mbk.nifty.com

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Stimulation of primary motor cortex for intractable deafferentation pain

Y. Saitoh, A. Hirayama, H. Kishima, S. Oshino, M. Hirata, A. Kato, and T. Yoshimine

Department of Neurosurgery, Osaka University Graduate School of Medicine, Osaka, Japan

Summary

To treat intractable deafferentation pains, we prefer stimulation of the primary motor cortex (M1). The methods of stimulation we utilize are electrical stimulation and repetitive transcranial magnetic stimulation (rTMS). In our department, we first attempt rTMS, and if this rTMS is effective, we recommend the patient to undergo procedures for motor cortex stimulation (MCS). A 90% intensity of resting motor threshold setting is used for rTMS treatment. In this study ten trains of 5 Hz rTMS for 10 seconds (50 seconds resting interval) were applied to the M1, S1, pre-motor and supplementary motor areas. Only M1 stimulation was effective for pain reduction in 10 of 20 patients (50%). Twenty-nine MCS procedures were performed by subdural implantation of electrodes, and in the case of hand or face pain, electrodes were implanted within the central sulcus (11 cases), because the main part of M1 is located in the central sulcus in humans. The success rate of MCS was around 63%, and seemed to be higher in cases of pain with spinal cord and peripheral origins, while it was lower in cases of post-stroke pain.

Keywords: Repetitive transcranial magnetic stimulation (rTMS); deafferentation pain; navigation; motor cortex; image-guided.

Introduction

Deafferentation pains are one of the most difficult types of pain to treat and are usually medically refractory. Only motor cortex stimulation (MCS) may provide pain relief in 50–75% of patients with deafferentation pains [6, 9, 11, 17]. Now, the primary motor cortex (M1) is a popular target for cortical stimulation as a method of treatment for medically refractory deafferentation pain [3, 5, 9, 11, 14, 15–17]. We have tried the sub-dural or intra-central sulcus implanting of electrodes to stimulate M1 more directly than is possible when using epidural techniques.

However, there have been few reports about the ability to relieve pain by stimulation of other adjacent cortical areas, for example, the postcentral gyrus (S1), supplementary motor area (SMA) and premotor area (preM). At our institute, we precisely applied repetitive transcranial magnetic stimulation (rTMS) to these areas, and compared the effectiveness of such treatments on pain relief.

Materials and methods

Patient profile

Twenty right-handed patients (14 males, 6 females, age ranging from 28 to 72 years) suffering from intractable deafferentation pain were treated with rTMS at Osaka University Hospital. There were 12 patients with post-stroke pain. Other origins of pain included two patients with spinal cord lesions, one with root avulsion, three with trigeminal nerve injuries, and two with peripheral nerve injuries. Patients had been administered with anti-convulsants, NSAIDs (non-steroidal anti-inflammatory drug), and anti-depressants and received psychological examinations and electroencephalogram (EEG) before rTMS to assess their potential for developing seizures. Informed consent was gained from all patients participating in this study, and approval was attained from the Ethics Committee of Osaka University Hospital.

Twenty-nine patients (25 males, 4 females, age ranging from 28 to 76 years) were treated with subdural or intra-central sulcus (11 cases) MCS. Of these, there were 16 patients with post-stroke pain. The other origins of pain included six brachial plexus injuries, three cases of phantom-limb pain, two cases of spinal cord lesions, one case of trigeminal neuropathic pain and one patient with pain related to pons injury. Five cases underwent both rTMS and MCS.

rTMS methods

rTMS was applied through a figure-of-eight coil which enabled a limited cortical stimulation, and which was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnosis A/S, Skovlunde, Denmark). At first, the resting motor threshold (RMT) of muscle corresponding to the painful area was determined by stimulation of M1. A 90% intensity of the RMT was used for treatment. Ten trains of 5 Hz rTMS for 10 seconds (50 seconds resting interval) were applied to the M1, S1, preM and SMA areas at random. A total of 500 stimuli were applied once in two days and the stimulation was done twice for each target. Sham stimulation was applied using previously reported methods [19]. The protocol used was in accordance with guidelines for the safe use of rTMS [20]. We used the Brainsight™ Frameless Navigation system (Rogure Research Inc, Montreal, Canada) which monitored the position and direction of the coil, and the position of the patient's head

Table 1. *Summary of 5 cases who underwent both rTMS and MCS*

Case	Age	Sex	Diagnosis	Pain duration	Pain area	rTMS	MCS
1	71	M	lt thalamic hemorrhage	5 y	rt hand	poor	poor
2	62	M	lt thalamic hemorrhage	8 y	rt hand	excellent	good
3	28	M	lt trigeminal neuropathic pain	2 y	lt face	excellent	good
4	29	M	ruptured spinal AVM	6 y	rt foot	excellent	good
5	59	M	rt putaminal hemorrhage	16 y	lt foot	good	good

Five cases who underwent both rTMS and MCS are summarized. Only Case 1 showed pain relief by neither rTMS nor MCS. The other cases showed pain relief by both rTMS and MCS. There were good correlations between the results of rTMS and those of MCS.

by attaching trackers with reflectors recognizable by an optical position sensor camera similar to those used in other MRI guided navigation systems [1, 4, 10]. Fixation and placement of the TMS coil were achieved by an articulated coil holder.

Evaluation of pain relief and statistical analysis

We obtained measurements of visual analogue scale (VAS) and the short form of McGill Pain Questionnaire (SF-MPQ) before, during, and after stimulation (15, 30, 60, 90 and 180 minutes) for each of the targets (sham, preM, SMA, M1, S1) from 20 patients, and evaluated the effectiveness of stimulations with analysis of variance in a two-way layout (patient and time). Moreover, we investigated the significance among the pain intensities experienced in the following eight successive evaluations (pre-stimulation, intra-stimulation, post-stimulation, post-15 minutes, post-30 minutes, post-60 minutes, post-90 minutes, post-180 minutes) with Wilcoxon matched-pairs signed-ranks test.

Results

rTMS

All of the patients received full courses of navigation-guided rTMS and there was no transient or lasting side effects involving convulsions. They were not able to distinguish sham stimulation from real rTMS. Effective treatment was defined as a VAS improvement of more than 30%. Ten of 20 patients (50%) showed significant reductions in pain on the VAS with M1 stimulation. Stimulation of other areas (S1, SMA, preM) did not provide effective forms of pain relief. Effectiveness continued significantly for three hours ($p < 0.05$, Wilcoxon matched-pairs signed-ranks test).

There were no significant differences in SF-MPQ scores. In the patients with high SF-MPQ scores, who mentioned property of their own in many item of SF-MPQ, the results of VAS and SF-MPQ demonstrated similar tendencies. On the other hand, in the patients with low SF-MPQ scores, there were only slight score changes in spite of VAS score reductions.

MCS

Of the 29 patients, 18 (62%) showed good or excellent pain relief with MCS. Seven of the 11 cases (64%) who underwent electrode implant within the central sulcus showed good or excellent results. In the five cases who underwent both rTMS and MCS, four rTMS responders showed successful results of MCS, while one poor-responder was not successful (Table 1).

Discussion

Recently rTMS has been applied as a treatment method for psychiatric and neuro-degenerative diseases such as depression [7], dystonia [18], schizophrenia, Parkinson's disease, seizures and so on [21]. Based on experiences with MCS, rTMS is now beginning to be applied to cases of intractable deafferentation pain [8, 13].

According to PET and fMRI [2, 12] studies, several areas in the normal brain are thought to participate in the perception of pain. We have tried rTMS of the M1, S1, SMA and preM areas and have compared the effects on pain relief. Only M1 stimulation was effective in 50% of the patients. Why stimulation of the M1 area is effective in the treatment of pain is still under debate. Probably, the several areas of the brain activated by M1 stimulation relieve pain in a comprehensive manner [3, 12, 17]. The mechanism of pain relief by rTMS might be almost the same as that of electrical stimulation [8].

Previous reports have described implantation of epidural electrodes over the precentral gyrus [5, 9, 11]. Such an approach might not provide optimal pain relief since both the method and the area of test stimulation were restricted by a brief operative period under local anesthesia. Our subdural implant or implant within the central sulcus seems to be more effective than that of the epidural implant, because our methods make it possible to stimulate M1 more directly.

The five cases who underwent both rTMS and MCS showed good correlations with pain relief. There are some differences between the detailed stimulation of rTMS and MCS. We consider that rTMS can anticipate the results of MCS (Table 1).

In conclusion, only 5 Hz stimulation of M1 is able to reduce intractable deafferentation pain in approximately one out of two patients. The pain reduction continued significantly for three hours. Today, rTMS may be a good predictor of MCS efficacy, and thus, we consider that MCS can be recommended to the patients with good results of rTMS. In the future, rTMS may take over from MCS as a treatment of deafferentation pain.

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Correspondence: Youichi Saitoh, Department of Neurosurgery, Osaka University Graduate School, 2-2 Yamadaoka, Suita-shi, Osaka 565-0871, Japan. e-mail: neurosaitoh@mbk.nifty.com

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eral missense and nonsense mutations have been identified in different part of the α1-subunit in autosomal dominant or recessive hyperekplexia (for review see Ref. [12]). The functional consequences of GLRA1 mutations are diverse and include loss of the α protein, inability to form glycine receptor complexes, inability to insert receptor complexes into the plasma membrane, changed sensitivity for ligand, and channel gating abnormalities.[12] The severe phenotype in these two children, with severe apneic attacks, is probably related to the recessive inheritance with total disturbance of correct folding of the β sheet of the M1 transmembrane domain.

The phenotype of the two children resembles the severe "major" form of HPX.[12] Patients with this form suffer from the triad of stiffness in the neonatal period, excessive startle reflexes and stiffness related to the startle reflex. The positive head-retraction reflex is very supportive clinical evidence of the diagnosis.[12] The severe apnoeic attacks seen here are rare, and as already mentioned above probably reflect recessive inheritance. The "major" form of HPX is usually due to mutations in GLRA1 or related genes.[12,13] Patients with the "minor" form only suffer from excessive startle reflexes without signs of stiffness. In the "minor" form the GLRA1 gene rarely shows mutations and the pathophysiological substrate of this form is still unclear.[12] Therefore, genetic screening for GLRA1 mutations should especially be performed in patients with the "major" form HPX. Usually, these patients have a positive family history with an autosomal dominant inheritance pattern; however this case illustrates the value of genetic screening in apparently sporadic or recessively inherited instances of the "major" phenotype.

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Motor Cortex Stimulation for Levodopa-Resistant Akinesia: Case Report

Naoki Tani, MD.[1] Youichi Saitoh, MD, PhD,[1]*
Haruhiko Kishima, MD, PhD,[1]
Satoru Oshino, MD, PhD,[1] Jun Hatazawa, MD, PhD,[2]
Kazuo Hashikawa, MD, PhD,[3] and
Toshiki Yoshimine, MD, PhD[1]

[1]Department of Neurosurgery, Osaka University Graduate School of Medicine, Osaka, Japan; [2]Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine, Osaka, Japan; [3]Human Brain Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan

Video

Abstract: **We treated a patient with levodopa-resistant akinesia with motor cortex stimulation (MCS), and she showed dramatic improvement more than 1 year. On admission, the patient presented severe akinesia and gait disturbance without tremor and rigidity, and did not respond to levo-**

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*Correspondence to: Dr. Youichi Saitoh, Department of Neurosurgery, Osaka University Graduate School of Medicne, Yamadaoka 2-2, Suita City, Osaka 565-0871, Japan. neurosaitoh@mbk.nifty.com

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