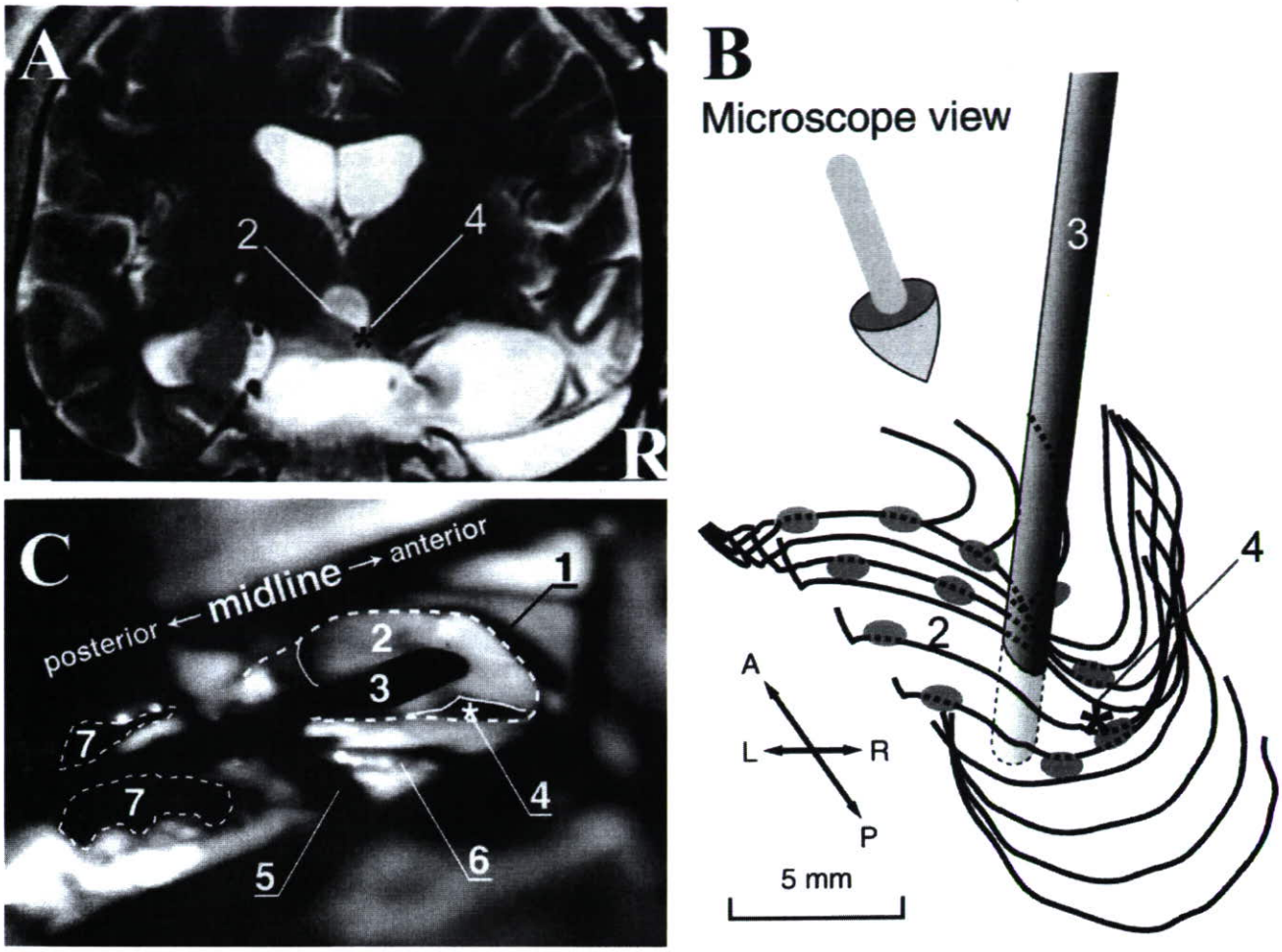

Fig. **2** Radiofrequency ablation of hypothalamic hamartoma (HH) under open craniotomy via a transcallosal subchoroidal approach. **A** MR image shows the morphology of the third ventricle and hamartoma. A bulge and notches in the floor of the third ventricle are formed by the hamartoma. **B** Reconstruction of the third ventricle floor for preoperative planning and intraoperative guidance. Gray circles indicate sites of electrode insertion and coagulation. A: anterior, P: posterior, R: right, L: left. **C** Intraoperative view shows insertion of the electrode into the HH. 1: foramen of Monro, 2: bulge of hamartoma, 3: electrode, 4: notch between the hamartoma and the right lateral wall of the third ventricle, 5: right thalamostriate vein, 6: anterior septal vein. 7: dissected surface of the massa intermedia.

usually does not appear until several months or years after irradiation [7]. When the first treatment is ineffective, a second treatment at least 36 months after the first is recommended [8]. Disconnection of the propagation pathway has recently been introduced into open surgery for HH, resulting in good seizure control [12]. However, postoperative complications are not likely to be infrequent [10]. To overcome the drawbacks of surgical resection and GKS, we applied RFA in the treatment of HH to reduce the epileptogenetic tissue and to disconnect the propagation discharge from the interface of the HH with the hypothalamus [9].

RFA for treatment of HH has been combined with stereotaxy. For small and ellipsoid HH a single tract is enough [1,13,14], but for large or irregularly shaped ones multiple ablations via multiple tracts are necessary [9]. In the present case, open RFA was performed under direct vision with the aid of a neuronavigation system [10,11], because the peculiar shape of this HH made it difficult to set up tracts of puncture, and even if the tract had been safely oriented, the electrode tip would have been likely to penetrate from the HH into the cistern, which might have caused an inadequate and irregular ablative lesion due to heat clearance. Complications in resective surgery occur by both ischemic and direct traumatic injury of the hypothalamus, which can be reduced in open RFA thus minimizing damage of the perforating hypothalamic arteries and the mobilization of HH. In a practical sense, we observed carefully the configuration of the floor of the third ventricle and used the bulge of the floor and the notches formed by the floor and lateral walls as anatomical landmarks.

When performing RFA, it is important to estimate the volume of the ablated area before the procedure. The volume of coagulation depends on various factors, e.g., the consistency, vascularity, and tissue dielectrics of the lesion, temperature of the probe tip, shape of the probe, and ablation time. On the basis of our experience with stereotactic RFA for another case of HH [9] and movement disorders, and of the experimental findings of other investigations [15], we assumed each ablated area in a single application to be ellipsoidal, measuring 3 × 6 mm in its greatest diameter after 60 seconds at 80 °C.

Conclusion

For the treatment of intractable epilepsy related to HH, RFA seems to effectively reduce its epileptogenetic potential and improve the epileptic status of the patient. It is less invasive than surgical resection, and its effect is immediate. Preoperative three-dimensional analysis of the lesion is necessary to enhance efficacy and ensure safety. However, the lack of long-term follow-up data restricts its application as an initial treatment. In addition, intraoperative monitoring of the ablated area should be established; we suggest an intraoperative MR study or ultrasonography for this purpose.

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Reduction of a Pancreatic Tumor after Total Removal of an ACTH Secreting Pituitary Tumor: Differential Diagnosis of Cushing's Syndrome

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Abstract. Endocrinologic tests sometimes fail to distinguish adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma from ectopic ACTH-secreting tumor. The authors experienced a case of Cushing's disease associated with a pancreatic tumor. Venous sampling contributed to the final diagnosis of Cushing's disease in this complex case, while endocrinologic tests showed paradoxical results. A 54-year-old woman presented with Cushing's syndrome and pancreatic tumor. Magnetic resonance imaging (MRI) failed to reveal a pituitary tumor, but a gadolinium-enhanced tumor with cystic components was seen in the pancreatic tail. Results of conventional endocrinologic tests suggested ectopic ACTH syndrome, but venous sampling including cavernous sinus sampling indicated an ACTH-secreting pituitary adenoma. Transsphenoidal surgery revealed a pituitary microadenoma, and total removal of the tumor was achieved. Postoperative abdominal MRI revealed that the pancreatic tumor diminished gradually without treatment. Selective cavernous sinus sampling was useful for distinguishing ACTH-secreting pituitary adenoma from ectopic ACTH syndrome in this complex case. This was a rare case in which the pancreatic tumor diminished after total removal of the ACTH-secreting pituitary adenoma.

Key words: Cushing's disease, Ectopic ACTH syndrome, Pancreatic neoplasm, Petrosal sinus sampling
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CUSHING'S disease accounts for approximately two-thirds of the cases of Cushing's syndrome [1]. Most patients of ACTH dependent Cushing's syndrome have adrenocorticotropic hormone (ACTH)-secreting pituitary microadenoma, but ectopic ACTH syndrome, which causes 9–18% of Cushing's syndrome [2], is sometimes responsible. Laboratory studies fail to accurately distinguish these two etiologies in 10–30% of cases [3–6], and the sensitivity of magnetic resonance imaging (MRI) for detection of ACTH-secreting pituitary microadenoma is reported to range from 54% to 91% [7–10]. Therefore, ectopic ACTH syndrome is sometimes misdiagnosed.

Herein, we describe a patient with ACTH-secreting pituitary adenoma and a mass in the pancreatic tail that was detected by abdominal MRI. Laboratory studies suggested ectopic ACTH syndrome, but selective cavernous sinus sampling (CSS) indicated the presence of ACTH-secreting pituitary adenoma. The pituitary adenoma was surgically removed and subsequently the pancreatic tumor decreased in size without any treatment. We discuss the difficult differential diagnosis in this case and describe the rare phenomenon that occurred after surgery.

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Case Report

Clinical findings and laboratory studies

A 54-year-old woman presented with central obesity, moon face, and muscle weakness. Cushing's syndrome was suspected, and she was admitted to Osaka University Hospital. Relevant laboratory values included sodium 148 mmol/l, potassium 2.9 mmol/l, fasting blood glucose 210 mg/dl, HbA1c 7.9%, and urinary 17 hydroxycorticosteroid 45.8 mg/day. Overnight low- (1 mg) and high-dose (8 mg) dexamethasone suppression tests showed lack of suppression of serum ACTH and cortisol levels, and there was no ACTH or cortisol response to intravenous injection of corticotropin-releasing hormone (CRH) (100 μg). The serum CRH level was 9.1 pg/ml (normal range: 3.2–14.7 pg/ml; Radio Immuno Assay method, SRL, Tokyo, Japan). After intravenous administration of 10 μg of desmopressin, the cortisol and ACTH levels did not increase significantly. The summary of clinical data including endocrinologic tests is shown in Table 1. On the basis of these laboratory findings, ectopic ACTH syndrome was suggested.

Table 1. Summary of preoperative clinical data including endocrine tests

Basic value		
ACTH (pg/ml)	121	
Cortisol (μg/dl)	47.7	
Urinary free cortisol (ng/dl)	1603	
17-OHCS (mg/day)	45.8	
17-KS (mg/day)	18	
ACTH daily rhythm	7:00	23:00
ACTH (pg/ml)	165	78
Cortisol (μg/dl)	47.7	33.1
CRH loading test	pre	post
ACTH (pg/ml)	193	154
Cortisol (μg/dl)	46.6	43.5
1mg Dexamethasone loading test	pre	post
ACTH (pg/ml)	165	—
Cortisol (μg/dl)	55.4	63
8mg Dexamethasone loading test	pre	post
ACTH (pg/ml)	270	—
Cortisol (μg/dl)	113.9	135.9
dDAVP loading test	pre	post
ACTH (pg/ml)	273	315
Cortisol (μg/dl)	—	121.7

17-OHCS, 17-hydroxycorticosteroid; 17-KS, 17-ketosteroid; dDAVP, desmopressin; pre, preload value; post, peak value after loading.

Imaging studies

MRI of the pituitary region, including dynamic study, failed to reveal microadenoma (Fig. 1A). Abdominal MRI revealed a 3 cm × 3 cm mass lesion of low intensity in the tail of the pancreas that was partly enhanced by gadolinium (Fig. 2A). Abdominal positron emission tomography with 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG-PET) showed an uptake area consistent with the location of the lesion (Fig. 3A). Endoscopic retrograde cholangiopancreatography revealed a solid and partly cystic mass lesion in the pancreatic tail with communication between the lesion and the main pancreatic duct. Accordingly, the pancreatic tumor was considered the most likely source of the ACTH.

Bilateral CSS of ACTH

Venous sampling was performed to determine the origin of the excessive serum ACTH. The catheter was

Fig. 1. (A) Preoperative head MRI. No apparent microadenoma was shown in the sella. (B) Postoperative head MRI. Fat tissue was replaced at the resected cavity.

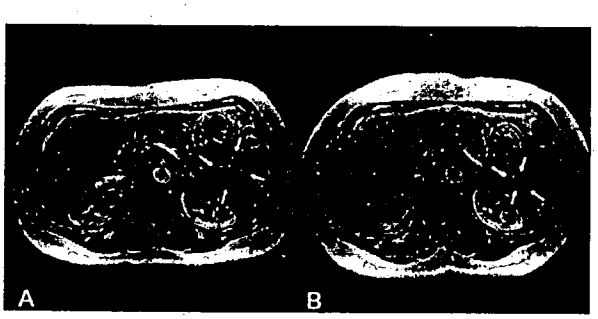

Fig. 2. Abdominal MRI with contrast enhancement
(A) Preoperative. A solid mass with cystic components was shown with contrast enhancement in the pancreatic tail. (B) Postoperative (7 months after operation). The mass diminished after the total removal of the ACTH secreting pituitary adenoma.

introduced from the right femoral vein and the blood samples were taken at several sites. The left inferior petrosal sinus (IPS) was hypoplastic, and a microcatheter was introduced into the cavernous sinuses from the right IPS. The levels of ACTH at the respective sites and the levels of prolactin (PRL), which was measured at both cavernous sinuses as reference to ensure adequate venous sampling, are shown in Table 2. The levels of ACTH in the inferior vena cava (peripheral to the junction with the bilateral renal veins), right cavernous sinus, and left cavernous sinus were 51, 242, and 302 pg/ml, respectively. The central-to-peripheral ratio of the serum ACTH level was 4.74 in the right cavernous sinus and 5.92 in the left. The left-to-right gradient was 1.24 and a normalized ACTH/PRL the left-to-right gradient was 1.34.

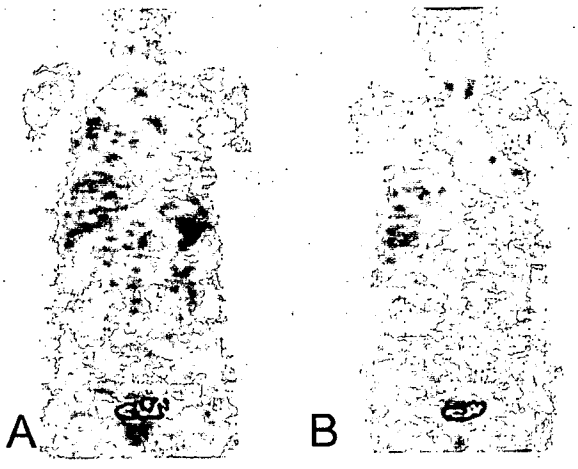

Fig. 3. (A) Preoperative FDG-PET. There is an uptake of FDG consistent with the tumor in the pancreatic tail. (B) Postoperative FDG-PET (4 months after operation). No uptake was shown in the same region.

Table 2. Summary of selective venous sampling

	ACTH (pg/ml)	Cortisol (μg/dl)	PRL (ng/ml)
IVC (peripheral of bilateral renal vein)	51	14.2	
lt. renal vein (peripheral of lt. adrenal vein)	42	10.6	
lt. renal vein (central of lt. adrenal vein)	41	10.8	
lt. adrenal vein	42	25.8	
hepatic vein	51	11.9	
rt. cavernous sinus	242		52.5
lt. cavernous sinus	302		48.8

IVC, inferior vena cava; rt, right; lt, left.

Neurosurgical intervention

Although the laboratory and abdominal MRI and FDG-PET findings suggested an ectopic ACTH-secreting tumor located in the pancreas, an ACTH-secreting pituitary adenoma was strongly suspected on the basis of the venous sampling. Therefore, the patient underwent transsphenoidal surgery. Upon opening of the dura of the sella on the left side, a grayish tumor was found. The tumor size seemed to be about 2 or 3 mm in diameter, which was compressed. The tumor and surrounding normal tissue were removed and the cavity was replaced by the abdominal fat. The postoperative MRI is shown in Fig. 1B. Histologic examination revealed a pituitary adenoma that was stained positively with ACTH antibody.

Postoperative course

Two weeks after surgery, daily cortisol secretion had normalized (15.1 μg/dl early in the morning and 4.9 μg/dl at midnight), and a dexamethasone (1 mg) suppression test decreased ACTH (from 26 pg/ml to 8 pg/ml) and cortisol (from 15.1 to 2.8 μg/dl) secretion. Moreover, the insulin loading test resulted in responsive increase of ACTH and cortisol (Table 3). But the response was poor, and it was considered to be compatible with postoperative status of cured Cushing's disease. Therefore, appropriate hydrocortisone replacement was administered to the patient for a while after surgery. The summary of the postoperative clinical data including endocrinologic tests is shown in Table 3.

Table 3. Summary of postoperative clinical data including endocrinologic tests

Basic value		
ACTH (pg/ml)	19	
Cortisol (μg/dl)	18.2	
Urinary free cortisol (ng/dl)	90	
17-OHCS (mg/day)	10.6	
17-KS (mg/day)	2.8	
ACTH daily rhythm	7:00	23:00
ACTH (pg/ml)	26	<5.0
Cortisol (μg/dl)	15.1	4.9
1mg Dexamethasone loading test	pre	post
ACTH (pg/ml)	26	8
Cortisol (μg/dl)	15.1	2.8
Insulin loading test	pre	post
ACTH (pg/ml)	9.7	14.8
Cortisol (μg/dl)	25	37

Interestingly, the pancreatic tumor decreased gradually in size (Fig. 2B), and FDG-PET showed diminished uptake at 4 months after surgery (Fig. 3B).

About two years after surgery, she has been free from any clinical symptom and the pancreatic tumor has never grown again on the subsequent radiological studies.

Discussion

In this case, it was difficult to distinguish ACTH-secreting pituitary adenoma from ectopic ACTH-secreting pancreatic tumor. The results of CSS provided the final diagnosis. After total removal of the ACTH-secreting adenoma the serum ACTH level normalized, and the patient was cured.

ACTH-secreting pituitary microadenoma cannot always be identified in imaging studies such as computed tomography [7, 11] and MRI [7–10] studies. Moreover, pituitary adenoma is detected incidentally by MRI in 10% of healthy persons; false positivity can also occur [12]. Non-invasive endocrine laboratory studies, including low- and high-dose dexamethasone suppression tests [4, 5], metyrapone stimulation [3], and peripheral CRH challenge tests [6], are often used to distinguish pituitary adenoma from ectopic sources of excessive ACTH. However, each of these tests fails to distinguish the two etiologies in 10–30% of cases [3–6]. Therefore, differential diagnosis of ACTH-dependent Cushing's syndrome remains, on occasion, a considerable clinical challenge.

Our patient, who presented with symptoms consistent with Cushing's syndrome, had a solid and partly cystic tumor in the pancreas and showed lack of suppression of serum ACTH and cortisol levels in the high-dose dexamethasone test and lack of ACTH and cortisol response to the CRH test. Therefore, ectopic ACTH syndrome was suspected. However, ectopic ACTH-secreting pancreatic tumor causing Cushing's syndrome is relatively rare, accounting for about 10% of all cases of ectopic ACTH syndrome and about 2% of all pancreatic endocrine tumors [13, 14]. Moreover, most ACTH-producing islet cell tumors are malignant, and the majority of cases involve liver metastasis by the time of diagnosis [15].

Association of pancreatic tumor with pituitary microadenoma is sometimes seen in cases of multiple endocrine neoplasia type 1 (MEN 1) [16, 17]. Yoshimoto *et al.* reviewed 106 cases of MEN 1 and reported that Cushing's disease was present in about 5% of patients [17]. Miyagawa *et al.* reported a case of MEN 1 consisting of Cushing's disease, primary hyperparathyroidism, and insulin-glucagonoma; the patient was treated successfully by transsphenoidal pituitary adenomectomy, subtotal parathyroidectomy, and enucleation of the pancreatic tumors [16].

Because we suspected an association of two different tumors in our case, we performed selective CSS even though endocrine laboratory studies suggested that an ectopic ACTH-secreting tumor in the pancreas was the likely cause of the excessive serum ACTH. CSS findings indicated the presence of an ACTH-secreting tumor, and thus CSS was very useful for distinguishing ACTH-secreting pituitary adenoma from ectopic ACTH syndrome in our case.

A number of studies have evaluated the role of venous sampling by microcatheter in the diagnosis of ACTH-dependent Cushing's syndrome [18–22]. Oldfield *et al.* reported that a central-to-peripheral ACTH ratio of greater than 2.0 has a sensitivity of 95% and specificity of 100% and after CRH administration the ratio of greater than 3.0 has a sensitivity and a specificity of 100% in inferior petrosal sinus sampling (IPSS) [18]. However, additional experience has revealed some false-negative results. Using the same cut-off value, a false-negative rate of 1–10% in patients with proven Cushing's disease has been reported [23–26]. False-negative results with IPSS have been attributed to wide variation of venous drainage [24]. Recently, Findling *et al.* suggested that the measurement of PRL (as an index of fidelity of pituitary venous effluent during IPSS) and the establishment of a normalized ACTH/PRL petrosal sinus to peripheral ratio will identify patients with Cushing's disease who fail to have a peak ACTH inferior petrosal sinus to peripheral ratio greater than 3.0 after CRH [27].

On the other hand, Teramoto *et al.* described the usefulness of CSS compared to IPSS and suggested that the tentative cutoff ratio is 5 for the diagnosis of pituitary lesions [19]. In our case, we obtained a ratio of greater than 5 in left cavernous sinus and fortunately the origin of excessive ACTH was in the pituitary gland. However, Teramoto *et al.* also reported that basal C/P ratios in the cavernous sinus exceeded 10 in most cases of Cushing's disease [19]. Taking these facts into consideration, for a more reliable diagnosis we should perform CSS after CRH administration or

measure the level of PRL from peripheral vein and cavernous sinus, and calculate a normalized ACTH/PRL petrosal sinus to peripheral ratio.

As for lateralization of the tumor in the pituitary gland, Oldfield *et al.* also reported that a greater than 1.4-fold difference in ACTH concentrations between the two inferior petrosal sinuses accurately localized the microadenoma in 68% of cases during basal sampling [18]. The accuracy of determining lateralization by means of bilateral inferior petrosal sinus sampling is reported to be approximately 75% [28], and that by means of bilateral CSS ranges widely from 40% to 94% [19, 29, 30]. In this case, the basal left-to-right gradient showed 1.24, but the normalized ACTH/PRL left-to-right gradient showed 1.34, which was near 1.4. Therefore, we opened the dura surrounding the sella on the left side. The pituitary adenoma was located on the left side of the pituitary gland and was totally removed. Therefore, it can be said that selective CSS is necessary for differential diagnosis of ACTH-dependent Cushing's syndrome, especially in cases of difficult differential diagnosis. Flitsch *et al.* also recommend CSS for diagnostic purposes in complex cases [31]. However, Suzuki *et al.* reported a rare case with an ACTH-producing ectopic pituitary adenoma in the sphenoid sinus [32]. Therefore, we should consider the possibility of such a case even if CSS indicated the pituitary origin as the more likely source of excessive ACTH.

It was interesting that the pancreatic tumor decreased in size. Unfortunately, histologic confirmation has not been obtained, but we speculate that the pancreatic tumor was hormone dependent because it diminished postoperatively with changes in the hormonal environment such as decreases in the serum ACTH and cortisol levels. In the literature, there was no report that a pancreatic tumor diminished after total removal of an ACTH producing pituitary adenoma. Ours is the first report of such a rare and interesting case.

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Research papers

Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex

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Abstract

The precentral gyrus (M1) is a representative target for electrical stimulation therapy of pain. To date, few researchers have investigated whether pain relief is possible by stimulation of cortical areas other than M1. According to recent reports, repetitive transcranial magnetic stimulation (rTMS) can provide an effect similar to that of electrical stimulation. With this in mind, we therefore examined several cortical areas as stimulation targets using a navigation-guided rTMS and compared the effects of the different targets on pain. Twenty patients with intractable deafferentation pain received rTMS of M1, the postcentral gyrus (S1), premotor area (preM), and supplementary motor area (SMA). Each target was stimulated with ten trains of 10-s 5-Hz TMS pulses, with 50-s intervals in between trains. Intensities were adjusted to 90% of resting motor thresholds. Thus, a total of 500 stimuli were applied. Sham stimulations were undertaken at random. The effect of rTMS on pain was rated by patients using a visual analogue scale (VAS) and the short form of the McGill Pain Questionnaire (SF-MPQ). Ten of the 20 patients (50%) indicated that stimulation of M1, but not other areas, provided significant and beneficial pain relief ($p < 0.01$). Results indicated a statistically significant effect lasting for 3 hours after the stimulation of M1 ($p < 0.05$). Stimulation of other targets was not effective. The M1 was the sole target for treating intractable pain with rTMS, in spite of the fact that M1, S1, preM, and SMA are located adjacently.

Keywords: Repetitive transcranial magnetic stimulation; Deafferentation pain; Navigation; Motor cortex; Image-guided

1. Introduction

Deafferentation pain is one of the most difficult types of pain to treat. Most cases of such pain are refractory to medical treatment. Only motor cortex stimulation (MCS) has been shown to provide any relief from deafferentation pain, and that relief is achieved in only 50–70% of patients (Meyerson et al., 1993; Nguyen et al., 1997; Saitoh et al., 2000; Katayama et al., 2003). While the mechanisms underlying the effects of MCS in reducing pain remain a topic of discussion, M1 is a popular target for cortical stimulation in the treatment of medically intractable deafferentation pain (Meyerson et al., 1993; Nguyen et al., 1997; Garcia-Larrea et al., 1999; Saitoh et al., 2000, 2003, 2004; Katayama et al., 2001, 2003; Rainov and Heidecke, 2003; Son et al., 2003).

The precentral gyrus (M1) or Broadmann's Area (BA) 4 is immediately anterior to the central sulcus. However, there have been few reports on the levels of pain relief achieved through precise stimulation with repetitive transcranial magnetic stimulation (rTMS) of such

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adjacent cortical areas as the postcentral gyrus (S1), premotor area (preM), and supplementary motor area (SMA).

Functional imaging studies such as by positron emission tomography (PET) and the mapping of evoked potentials with subdural grid electrodes have shown that pain-related activation occurs not only in M1 but also in S1, preM, SMA, and other areas (Coghill et al., 1999; Peyron et al., 2000; Ohara et al., 2004). In addition, M1 itself provides some modulation of the preM and SMA (Bestmann et al., 2003). According to recent reports (Lefaucheur et al., 2001, 2004; Kanda et al., 2003; Topper et al., 2003; Tamura et al., 2004; Pleger et al., 2004), rTMS of M1 provides an effect similar to that of the electrical stimulation of M1 in patients with medically intractable deafferentation pain. However, it is not easy to repeatedly stimulate the same cortical area, and the results of stimulation tend to vary. In addition, the electrical current evoked by rTMS is generally confined to the cortex (Sekino and Ueno, 2004). For these reasons, we attempted navigation-guided rTMS on the patients with intractable deafferentation pain to precisely stimulate the cerebral cortical areas. The aim of this study was to assess whether M1 is the only target for treating medically refractory deafferentation pain.

2. Materials and methods

2.1. Subjects

Subjects comprised of 20 right-handed patients (13 men, 7 women; age 28 to 72 years, mean 56.8 years) suffering from intractable deafferentation pain. Twelve of the patients suffered from post-stroke pain; strokes were due to thalamic hemorrhage or infarction ($n = 7$), putaminal hemorrhage ($n = 4$), and pontine hemorrhage ($n = 1$). Deafferentation pain originated from a spinal cord lesion in two cases (one due to injury and one due to infarction), from trigeminal neuropathic pain in three cases (one due to dental trouble, one due to cavernous cavernoma operation, and one due to herpetic infection), from a brachial plexus injury ($n = 1$), from a peripheral neuroma operation ($n = 1$), and from a cauda equina lesion ($n = 1$). Patient characteristics are shown in Table 1. Patients were administered anti-convulsants, NSAIDs (non-steroidal anti-inflammatory drugs), and anti-depressants as required. Patients also underwent psychological examination and electroencephalography (EEG) examinations before rTMS to assess whether seizure development was likely. Informed consent was obtained from all study participants. This study was approved by the Ethics Committee of Osaka University Hospital, and all patients were blinded to the area being stimulated and to the expected effect.

2.2. rTMS

rTMS was applied through a figure-eight coil (MC B-70, Medtronic Functional Diagnosis A/S, Skovlunde, Denmark), which provides for limited cortical stimulation. The coil was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnosis A/S). First, the resting motor threshold of the affected muscle area was determined by stimulation of the corresponding M1 area. The resting motor threshold at 90% intensity was used for treatment. We determined the resting motor threshold based on the EMGs in the affected area. Muscle twitches in painful areas can be elicited, if stimulated carefully according to the somatotopy. This is possible even with trigeminal lesion and lower limbs. For the patients in whom muscle twitches in the painful areas were difficult to elicit due to severe damage of motor pathways, rTMS was applied with an intensity at 100 A/μs. In our study, 100 A/μs was the maximum tolerable

Table 1
Patient characters and the results of VAS after rTMS are summarized

Case	Age (years)	Sex	Diagnosis	Pain duration (years)	Pain area	VAS reduction M1 rTMS (%)	Medications
1	55	F	Left spinal cord infarction	2.6	Left lower limb	−52.6	NSAID, AC
2	57	F	Left putaminal hemorrhage	5	Right lower limb	−47.1	NSAID, AC, AD
3	71	F	Left thalamic hemorrhage	1.5	Right upper limb	−60	NSAID, AC, AD
4	70	M	Left thalamic hemorrhage	4.4	Right upper limb	10	NSAID, AA, AC
5	62	M	Left thalamic hemorrhage	8.5	Right upper limb	−66.7	NSAID, AA, AC
6	70	M	Left thalamic hemorrhage	4.3	Left upper limb	0	NSAID, AC
7	63	M	Left thalamic infarction	5	Right upper limb	0	NSAID, AC, AD
8	28	M	Left trigeminal neuropathic pain	1.6	Left face (nV2)	−57.1	NSAID, AD, morphine
9	43	F	Left pontine hemorrhage	4.3	Right lower limb	0	NSAID, AC, AD
10	41	M	Cauda equina lesion	6.3	Right lower limb	−80	NSAID, AA, AC, AD
11	52	F	Left thalamic hemorrhage	2	Right upper limb	−12.5	NSAID, AA, AD
12	69	F	rt. trigeminal neuropathic pain	13.9	Right face (nV1 ~ V3)	−12.5	NSAID, AA, AC, AD
13	41	M	spinal cord injury	2.9	Left upper limb	−20	NSAID, AA
14	45	M	Left putaminal hemorrhage	1.3	Right upper limb	0	NSAID, AA, AC, AD
15	66	M	Right trigeminal neuropathic pain	8.5	Right face (nV3)	0	NSAID, AC
16	51	M	Left putaminal hemorrhage	1.6	Right upper limb	0	NSAID, AC
17	72	M	brachial plexus injury	11.1	Left upper limb	−33.3	NSAID, AD
18	59	M	Right putaminal hemorrhage	16	Left lower limb	−60	NSAID, AA
19	51	F	Peripheral nerve lesion	24.3	Left lower limb	−33.3	NSAID, AA, AD
20	70	M	Left thalamic infarction	2.2	Right upper limb	−36.8	NSAID, AA, AC, AD

Abbreviations: F, female; M, male; AA, antianxiety drugs; AC, anticonvulsants; AD, antidepressants; NSAID, non-steroidal anti-inflammatory drugs.

intensity for most patients, with higher intensities resulting in scalp pain. A potential equivalent to 90% of the intensity of the resting motor threshold was used for treatment. Ten trains of 10-s 5-Hz TMS pulses, with 50 s intervals between trains, were applied to the M1, S1, preM, and SMA at random. Thus, a total of 500 stimulations (10 trains × 5 Hz × 10 s) of each of the targets were applied once in 2 days, therefore, time intervals were about 48 h. All targets were stimulated in random order. Sham stimulation was applied as described in previous literature (Tamura et al., 2004). In brief, parameters were the same as in actual stimulations, but the coil was placed at a 45° angle to the skull, and synchronized electrical stimulations were delivered to the forehead.

Somatotopy was supposed on M1 and S1, as estimated by MRI. In the S1 stimulation, we stimulated target areas (relating to the painful body part) carefully according to the somatotopic mapping of the face, upper limb area, and lower limb areas. The premotor area (BA6) and supplemental motor area (BA8) are adjacent to the M1. Targeting of BA6 and BA8 was performed using an MRI based navigation system of the individual's brain surface.

This protocol is in compliance with the guidelines for the safe use of rTMS (Wassermann, 1998). The TMS coil was held and positioned by an articulated coil holder.

2.3. Navigation system

The Brainsight™ Frameless Navigation system (Rogue Research Inc, Montreal, Canada) was used to monitor the position and direction of the coil, and the position of the patient's head. Trackers with reflectors recognized by the optical position sensor camera were attached as with other MRI-guided navigation systems (Boroojerdi et al., 1999; Herwig et al., 2001; Neggers et al., 2004). The Brainsight™ frameless navigation system differs from other navigation systems in that it can, with high anatomical accuracy, superimpose the location and angle of the coil on a 3D-image of an individual's cortical surface with high anatomical accuracy based on the MRI of that individual (Fig. 2).

2.4. Evaluation of pain relief

The intensity of pain was evaluated in all patients before, during, and after (at 0, 30, 60, 90, and 180 min) rTMS or sham stimulation by means of a visual analogue scale (VAS) and the short form of the McGill Pain Questionnaire (SF-MPQ).

2.5. Stimulation area

We selected four cortical targets for navigation-guided rTMS: M1, S1, preM, and SMA. Stimulation of these areas is thought to possibly reduce pain because functional imaging studies have suggested involvement of these areas in pain perception.

2.6. Statistical analysis

We compared the intensities of pain reported by VAS score before, during, and after (at 0, 30, 60, 90, and 180 min) stimulation of each of the targets (sham, M1, S1, preM, and SMA). Differences were analyzed with a two-way analysis of variance and the Wilcoxon matched-pairs signed-rank test (area and time).

3. Results

All 20 patients underwent all planned sessions of navigation-guided rTMS and no transient or lasting side effects, including convulsion, were observed. The patients were unable to distinguish sham stimulation from actual rTMS, because the synchronized electrical stimulation applied to the forehead made the forehead spasm, as was the case with actual TMS.

Stimulation was judged to be effective if there was an improvement in the VAS score of more than 30%. Ten of the 20 patients (50%) showed pain reduction as indicated by the VAS scores. The only target that had a significant effect on pain, as indicated by the VAS scores, was M1 ($p < 0.01$, two-way analysis of variance). A significant reduction in pain was observed for 3 h ($p < 0.05$, Wilcoxon matched-pairs signed-rank test) (Fig. 1). There were no significant differences between the effects of S1, preM or SMA rTMS or of sham stimulation, according to VAS scores.

rTMS did not produce a constant change in SF-MPQ scores. In the patients with a high SF-MPQ score of baseline pain, the results of VAS and SF-MPQ tended to be similar. In those with a low SF-MPQ score of baseline pain, scores changed little, despite the reduction in VAS scores.

After rTMS, pain returned gradually. However, one patient felt comfortable for 2–3 days because of a decrease in severe pain.

4. Discussion

rTMS has been applied recently as a method of treatment for psychiatric and neuro-degenerative diseases such as depression (Kimbrell et al., 1999; Speer et al., 2000; Padberg et al., 2002), dystonia (Siebner et al., 2003), schizophrenia, Parkinson's disease, and seizures (Wassermann and Lisanby, 2001; Kobayashi and Pascual-Leone, 2003). On the basis of MCS results, rTMS is now being applied to intractable deafferentation pain (Lefaucheur et al., 2001, 2004; Pleger et al., 2004).

The detailed mechanism underlying pain relief by MCS is controversial. According to PET activation studies, pain relief by MCS appears to activate several brain areas participating in pain perception (Garcia-Larrea et al., 1999; Saitoh et al., 2004). A common finding in patients with post-stroke pain was a relative decrease in thalamic rCBF during chronic pain, which receded after MCS. We have previously reported on activation of the cingulate gyrus and left posterior thalamus by right MCS (Saitoh et al., 2004). Garcia-Larrea et al. (1999) reported that MCS might activate cingulate,

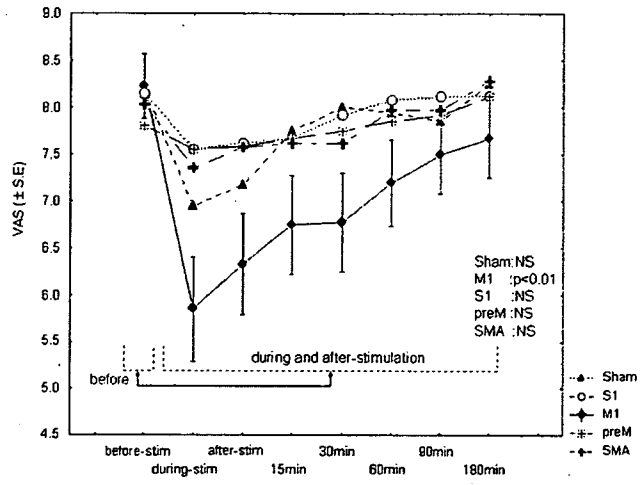

Fig. 1. Ten of 20 patients (50%) showed pain reduction as indicated by the VAS scores. This figure shows average VAS scores over all subjects. The only effective target was M1 ($p < 0.01$, two-way analysis of variance). A significant effect was observed for 3 h ($p < 0.05$, Wilcoxon matched-pairs signed-rank test). There were no significant reductions in pain after S1, preM or SMA rTMS or after sham stimulation. Error bars represent SE. ···▲···, sham stimulation; –○–, S1 (postcentral gyrus) stimulation; –✦–, M1 (precentral gyrus) stimulation; -✳-, preM (premotor area) stimulation; -✦-, SMA (supplementary motor area) stimulation.

orbitofrontal cortex, and upper brain stem regions of the brain. The mechanism behind of pain relief through rTMS may be similar to that of MCS (Kimbrell et al., 2002).

M1 has become a major target for electrical stimulation, however, it is still unclear whether stimulation of other cortical areas (S1, S2, preM, SMA, etc.) may be more effective for pain relief. Topper et al. (2003) tried rTMS (15 Hz, 110%, 2 s) in two patients with brachial plexus avulsion, and pain reduction was obtained by stimulation of the posterior parietal cortex (P3, P4 by the 10–20 EEG method), with effects continuing for up to 10 min. Kanda et al. (2003) applied TMS over the sensory motor cortex, occipital cortex, S2, and medial frontal cortex, and suggested that TMS to the S1/M1 can facilitate central processing of pain perception whereas stimulation over the medial frontal cortex suppresses this processing. However, their targets were identified by the 10–20 EEG method. S2 is rather large area and targeting it is difficult. While worth studying, our results indicated that the effectiveness of stimulating targets other than M1 may not be so high.

High-frequency rTMS enhances neuronal firing efficacy, and low-frequency rTMS has the opposite effect (Kimbrell et al., 1999; Speer et al., 2000). Lefaucheur et al. (2001) tried rTMS at two different frequencies (10 and 0.5 Hz) in 18 patients with intractable unilateral hand pain. The VAS score improved at 10 Hz, but did

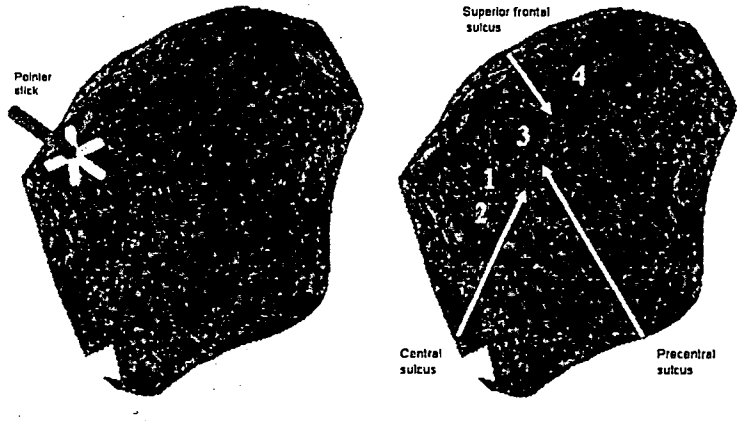

Fig. 2. The navigation system can superimpose the location and angle of the coil in relation to the cortical surface of an individual in real time on their MRI with high anatomical accuracy. The precentral gyrus (M1) (1), and postcentral gyrus (S1) (2) both representing hand areas, the premotor area (3) and the supplementary motor area (SMA) (4) are selected as typical target examples. A superimposed pointer stick represents the center of the figure-eight coil and demonstrates not only the location but also the angle to the cortex surface of the coil in real time consistently on MRI of individuals.

not at 0.5 Hz. In addition, good pain control by high-frequency stimulation (10–20 Hz) has been reported in some rTMS studies (Topper et al., 2003; Pleger et al., 2004). Effectiveness of low frequency (1 Hz) rTMS was reported only by Tamura et al. (2004) in normal subjects with acute pain caused by capsaicin.

Siebner et al. (2000) reported that sustained increases of rCMRglc were recognized bilaterally in M1 and SMA on FDG-PET study at subthreshold 5-Hz rTMS of M1. The fMRI study demonstrated that subthreshold high-frequency stimulation modulates the communication between the cortex and remote frontal area, and that suprathreshold rTMS modulates the stimulated area itself (Bestmann et al., 2003).

The effect of rTMS may be dependent on the cause of pain. From our results, the response of post-stroke pain to rTMS seemed to be low. It was reported that the factors most favorable for rTMS treatment are a trigeminal nerve lesion and the presence of sensation in the painful zone, and those least favorable are brain stem stroke, limb pain, and severe sensory loss (Lefaucheur et al., 2004).

Previous reports showed that pain relief by rTMS continued up to 10 min (Topper et al., 2003; Tamura et al., 2004). Because CMRglc changes on PET and BOLD effects on fMRI do not continue for more than several seconds following TMS (Siebner et al., 2000; Bestmann et al., 2003), the effect of rTMS has been thought to disappear with cessation of the stimulation. In our study, pain relief continued for 3 h. A change in the affective-emotional component of chronic pain may have the greatest influence in providing pain relief.

Some groups (Lefaucheur et al., 2001, 2004; Pleger et al., 2004) have determined the M1 target area corresponding to the hand or foot by the basis of muscle twitching caused by single-pulse TMS. Other groups have determined the stimulation site by the 10–20 EEG method (Kanda et al., 2003; Topper et al., 2003) or by measuring the distance along a para-sagittal line from the targeted motor area (Siebner et al., 2000; Speer et al., 2000; Kimbrell et al., 2002; Padberg et al., 2002). Their stimulations were usually done by freehand. We believe that it is very difficult to apply all stimulations in the same position for rTMS. We, therefore, performed rTMS using a frameless navigation system in accordance with the patient's own cortical anatomy. The TMS coil was positioned by an articulated coil holder. Without navigation system, even identification of M1 is difficult in patients with severe motor weakness whose evoked motor response is barely induced by a single TMS. The anatomical error of the navigation system is considered to be less than about 5 mm. This is based on the observation that muscle twitches did not occur, if the coil was out of position by about 1 cm on the MRI guided navigation system. Experimental simulation showed that the electrical current induced with the figure-eight coil is considerably limited in the cortex (Sekino and Ueno, 2004). We wish to emphasize that navigation system is indispensable for rTMS.

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Reduction of intractable deafferentation pain due to spinal cord or peripheral lesion by high-frequency repetitive transcranial magnetic stimulation of the primary motor cortex

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Object. The authors previously reported that navigation-guided repetitive transcranial magnetic stimulation (rTMS) of the precentral gyrus relieves deafferentation pain. Stimulation parameters were 10 trains of 10-second 5-Hz TMS pulses at 50-second intervals. In the present study, they used various stimulation frequencies and compared efficacies between two types of lesions.

Methods. Patients were divided into two groups: those with a cerebral lesion and those with a noncerebral lesion. The rTMS was applied to all the patients at frequencies of 1, 5, and 10 Hz and as a sham procedure in random order. The effect of rTMS on pain was rated by patients using a visual analog scale.

Results. The rTMS at frequencies of 5 and 10 Hz, compared with sham stimulation, significantly reduced pain, and the pain reduction continued for 180 minutes. A stimulation frequency of 10 Hz may be more effective than 5 Hz, and at 1 Hz was ineffective. The effect of rTMS at frequencies of 5 and 10 Hz was greater in patients with a noncerebral lesion than those with a cerebral lesion.

Conclusions. High-frequency (5- or 10-Hz) rTMS of the precentral gyrus can reduce intractable deafferentation pain, but low-frequency stimulation (at 1 Hz) cannot. Patients with a noncerebral lesion are more suitable candidates for high-frequency rTMS of the precentral gyrus. *(DOI: 10.3171/JNS-07/09/0555)*

KEY WORDS • **deafferentation pain** • **imaging-guided navigation** • **motor cortex** • **repetitive transcranial magnetic stimulation**

DEAFFERENTATION or neuropathic pain caused by a cerebral, spinal cord, or peripheral lesion is one of the most difficult types of pain to treat, and most cases are refractory to medical treatment. Only MCS has been shown to provide relief in cases of such deafferentation pain, and relief is achieved in only 50 to 70% of patients.[4,9,11,18] The mechanism underlying the effects of MCS in reducing pain remains controversial. However, the precentral gyrus is a common target for cortical stimulation in the treatment of medically intractable deafferentation pain.[1,4,9,11,14,16–18] According to recent reports,[3,7,8,13,21,22] rTMS of the precentral gyrus provides an effect similar to that of MCS in patients with medically intractable deafferentation pain. However, it can be difficult to stimulate the same cortical area repeatedly, and results tend to vary. In addition, the electric current evoked by rTMS is generally confined to the cortex.[19] For these reasons, we have used navigation-guided rTMS in patients with intractable deafferentation pain to precisely stimulate specific cerebral cortical areas.

We have previously reported that navigation-guided 5-Hz rTMS of the precentral gyrus significantly reduced intractable neuropathic pain in 50% of patients.[2] We selected four cortical targets for navigation-guided rTMS: the precentral gyrus, the postcentral gyrus, the premotor cortex, and the supplementary motor area. However, only stimulation of the precentral gyrus produced pain relief. In addition to the cortical target for rTMS, the stimulation parameters and the type of lesion are important. In the present study, we varied the stimulation frequency for navigation-guided rTMS of the precentral gyrus and compared the efficacies of the various frequencies, particularly between origins of pain.

Abbreviations used in this paper: ANOVA = analysis of variance; MCS = motor cortex stimulation; rTMS = repetitive transcranial magnetic stimulation; SF-MPQ = short-form McGill Pain Questionnaire; VAS = visual analog scale.

Clinical Material and Methods

Patient Population

The patient population comprised 13 right-handed patients (seven men and six women; age range 29–76 years,

mean age 59.4 years) suffering from intractable deafferentation pain. Seven of the patients were suffering from poststroke pain due to thalamic hemorrhage or infarction (three), or putaminal hemorrhage (four). Two patients were suffering from deafferentation pain originating from a spinal cord lesion (ruptured arteriovenous malformation or infarction), and one patient each was suffering from pain due to brachial plexus injury, peripheral nerve injury, a cauda equina lesion, or a phantom limb. Patient characteristics are listed in Table 1. Patients were assigned to one of two groups according to the type of lesion: cerebral lesion, or spinal cord or peripheral lesion (noncerebral lesion). Patients were given anticonvulsants, nonsteroidal anti-inflammatory drugs, and antidepressants, as needed and also during the rTMS sessions. Patients also underwent psychological examination and electroencephalographic examination before rTMS to assess whether seizure development was likely. Patients who experienced pain reduction in response to 5-Hz stimulation were enrolled in this study. Informed consent was obtained from all study participants. The study was approved by the Ethics Committee of Osaka University Hospital, and all patients were blinded to the area being stimulated and to the expected effect.

TABLE 1

*Characteristics of patients experiencing intractable deafferentation pain**

Case No.†	Age (yrs), Sex	Diagnosis	Pain	
			Duration (yrs)	Location
1	59, M	rt putaminal hemorrhage	16	lt lower limb
2	57, F	lt putaminal hemorrhage	5	rt lower limb
3	62, M	lt thalamic hemorrhage	8.5	rt upper limb
4	70, M	lt thalamic infarction	2.2	rt upper limb
5	64, F	lt putaminal hemorrhage	6.9	rt lower limb
6	74, F	lt putaminal hemorrhage	35	rt lower limb
7	76, F	lt thalamic infarction	2	rt upper limb
8	55, F	spinal cord infarction	2.6	lt lower limb
9	29, M	ruptured spinal AVM	5.5	rt lower limb
10	62, M	phantom limb pain	7	bilat lower limbs
11	41, M	cauda equina lesion	6.3	rt lower limb
12	72, M	lt brachial plexus injury	11	lt upper limb
13	51, F	peripheral nerve injury	24.3	lt lower limb

* AVM = arteriovenous malformation.

† The patients in Cases 1 to 7 experienced neuropathic pain due to a cerebral lesion, and those in Cases 8 to 13 had neuropathic pain due to a spinal cord or peripheral lesion.

The rTMS Procedure

The rTMS was applied through a figure-eight coil (MC B-70, Medtronic Functional Diagnostics A/S), which provides limited cortical stimulation. The coil was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnostics A/S). The resting motor threshold of the affected muscle area was determined by stimulation of the corresponding precentral gyrus area and electromyography in the affected area. The resting motor threshold at 90% intensity was used for treatment. Muscle twitches can be elicited in painful areas, if stimulated carefully according to somatotopy. This is possible even with trigeminal lesions and in the lower limbs. For patients in whom muscle twitches in painful areas were difficult to elicit due to severe damage of motor pathways, rTMS was applied with an intensity of 100 A/μsec. This was the maximum tolerable intensity for most patients in our study, with higher intensities resulting in scalp pain.[2] A potential equivalent to 90% of the intensity of the resting motor threshold was used for treatment. Ten trains of 10-second 5-Hz TMS pulses with 50-second intervals between trains, five trains of 10-second 10-Hz TMS pulses with 50-second intervals between trains, continuous 1-Hz TMS pulses for 500 seconds, and sham 5-Hz TMS pulses were applied to the precentral gyrus in random order. A total of 500 stimulations were applied for each parameter, and there was an interval of about 48 hours before each new series of stimulations was performed. Sham stimulation was applied as described previously.[2,21] In brief, the parameters were the same as for actual stimulations, but the coil was placed at a 45° angle to the skull, and synchronized electrical stimulations were delivered to the forehead. The protocol was in compliance with the Guidelines for the Safe Use of rTMS.[23] The TMS coil was held and positioned by an articulated coil holder. The Brainsight Frameless navigation system (Rogue Research Inc.) was used to monitor the position and direction of the coil and the position of the patient's head, as described previously.[2]

Evaluation of Pain Relief

Using a VAS and the SF-MPQ, the patients evaluated their own pain before and after (at 0, 15, 30, 60, 90, and 180 minutes) rTMS (at 1, 5, and 10 Hz) or sham stimulation.

Statistical Analysis

We evaluated the effectiveness of stimulation for each patient according to the reduction rate of VAS scores (reduction rate = $1 - VAS_{poststimulation}/VAS_{prestimulation}$). We evaluated the influence of the various frequencies (sham, and 1, 5, and 10 Hz) and lesion types by applying repeated-measures ANOVA to the reduction rate of VAS. To compare sham stimulation with rTMS (at 1, 5, and 10 Hz), we used the Dunnett multiple-comparisons at various points after stimulation (Fig. 1).

Results

All 13 patients participated in all planned sessions of navigation-guided rTMS, and no transient or lasting side effects, including convulsion, were observed. Patients were unable to distinguish sham stimulation from rTMS because the synchronized electrical stimulation applied to the forehead induced forehead spasms. All 13 patients underwent sham stimulation and 1-, 5-, and 10-Hz rTMS of the precentral gyrus. Repeated-measures ANOVA indicated that the frequency of stimulation ($p = 0.03$) and the presence or absence of a cerebral lesion ($p = 0.04$) contributed to pain reduction as judged by the reduction rate of VAS scores. Interaction between these factors was not significant ($p = 0.80$). The reduction rates of VAS scores for each frequency are shown in Fig. 1. Stimulations at 5 and 10 Hz, compared with sham stimulation, were effective in reducing pain for up to 180 minutes ($p < 0.05$, repeated-measures ANOVA). Stimulation at 1 Hz did not differ from sham stimulation. In the cerebral lesion group, 5- and 10-Hz

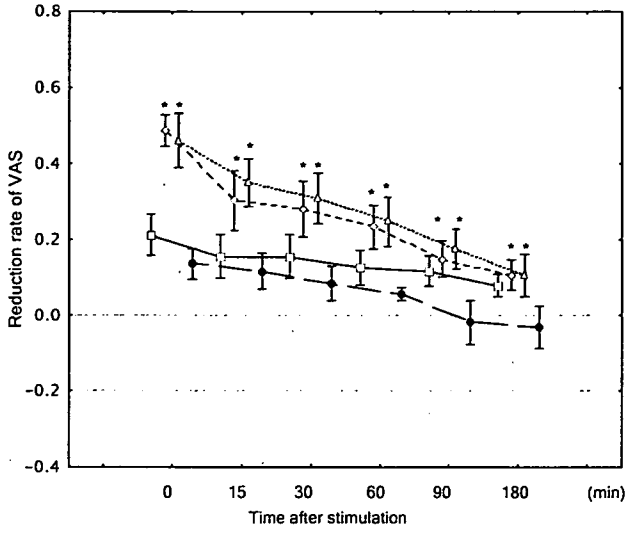

FIG. 1. Graph showing the reduction rate of VAS in all 13 patients after sham stimulation and 1-, 5- and 10-Hz rTMS of the precentral gyrus. As a result of repeated-measures ANOVA, the frequency of stimulation and the presence or absence of a cerebral lesion contributed to pain reduction as determined by a decrease in the VAS. Patients exhibited significant pain reduction after 5- and 10-Hz rTMS (but not after 1-Hz rTMS) compared with sham stimulation until 180 minutes, as indicated by the VAS scores. The VAS scores are presented as the means ± standard error of the means (SEMs). *$p < 0.05$. *Circles* denote sham stimulation; *squares*, 1-Hz rTMS; *diamonds*, 5-Hz rTMS; and *triangles*, 10-Hz rTMS.

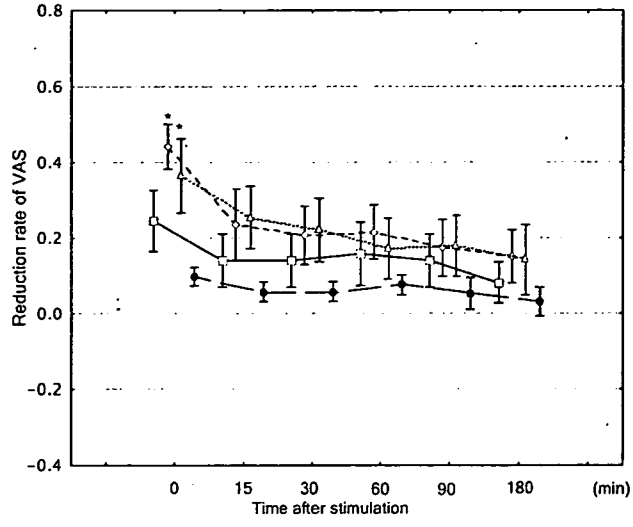

FIG. 2. Graph showing the reduction rate in VAS scores in the cerebral lesion group (seven patients). According to the Dunnett multiple-comparisons procedure, rTMS at 5 and 10 Hz, compared with sham stimulation, significantly reduced pain as determined by the reduction rate of VAS score only just after rTMS. The VAS scores are presented as the means ± SEMs. *$p < 0.05$.

rTMS, in comparison to sham stimulation, resulted in significant pain reduction just after rTMS ($p < 0.05$, according to Dunnett multiple-comparisons), and the mean reduction in VAS scores just after rTMS was greater than 30% (Fig. 2). In the noncerebral lesion group, 5- Hz rTMS resulted in significant pain reduction at 0, 30, and 90 minutes after rTMS ($p < 0.05$), and the mean reduction in VAS scores was greater than 30% for up to 30 minutes. The rTMS at 10 Hz, compared with sham stimulation, resulted in significant pain reduction for up to 90 minutes ($p < 0.05$), and the mean reduction in VAS scores was greater than 30% for up to 60 minutes (Fig. 3). The rTMS did not produce a consistent change in SF-MPQ scores. In patients with a high baseline SF-MPQ score (> 20), the VAS and SF-MPQ scores tended to be similar. In patients with a low baseline SF-MPQ score (< 10), the SF-MPQ score changed little, regardless of a reduction in the VAS score.

Discussion

In our previous study,[2] only 5-Hz rTMS of the precentral gyrus, compared with rTMS of adjacent cortical areas (the postcentral gyrus, the premotor cortex, and the supplementary motor area), relieved pain. Appropriate stimulation parameters (for example, stimulation frequency) have remained uncertain. In the present study, 5- and 10-Hz rTMS of the precentral gyrus were significantly more effective than sham stimulation, but 1-Hz rTMS was not. The rTMS may be more effective at 10 Hz than at 5 Hz (Figs. 1–3). Correlation between the efficacy of rTMS and type of lesion was also investigated. Deafferentation pain caused by a cerebral lesion was more refractory to rTMS than that caused by a spinal cord or peripheral lesion (Figs. 2 and 3).

Pain reduction in response to rTMS of the precentral gyrus was likely due to modification of pain perception, as previously reported.[3,13] The detailed mechanism underlying pain relief in response to MCS was examined by positron emission tomography activation studies.[1,17] The MCS ap-

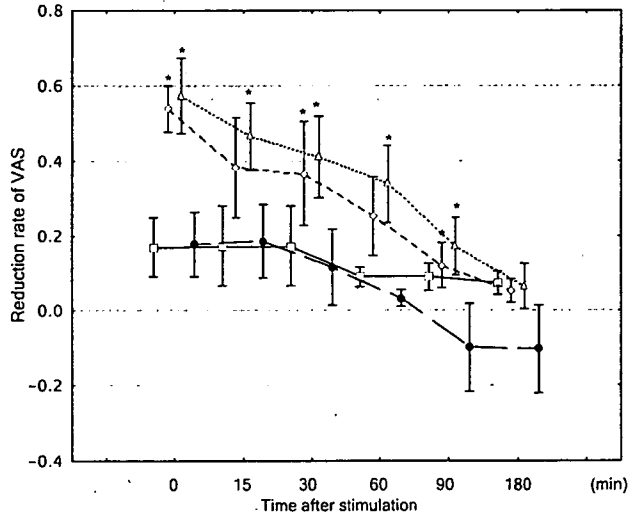

FIG. 3. Graph showing the reduction rate of VAS scores in the noncerebral lesion group (six patients). According to the Dunnett multiple-comparisons procedure, rTMS at 5 Hz significantly reduced pain as determined by the decrease in VAS score at 0, 30, and 90 minutes; rTMS at 10 Hz significantly reduced pain for up to 90 minutes. The reduction rate of the VAS score for 10 Hz was greater than that for 5 Hz at each time point after stimulation. The VAS scores are presented as the means ± SEMs. *$p < 0.05$.

pears to activate several brain areas involved in pain perception.[1,17] A common finding in patients with poststroke pain was a relative decrease in thalamic regional cerebral blood flow during chronic pain.[12] We previously reported activation of the anterior cingulate gyrus and left posterior thalamus in response to right MCS.[17] Garcia-Larrea et al.[1] reported that MCS may activate cingulate, orbitofrontal cortex, and upper brainstem regions. The mechanism underlying pain relief in response to high-frequency rTMS may be similar to that of MCS.[5] Several brain regions associated with pain perception may be activated by subthreshold high-frequency rTMS of the precentral gyrus and may reduce deafferentation pain comprehensively.

High-frequency rTMS enhances neuronal firing efficacy, and low-frequency rTMS has the opposite effect.[6,20] The rTMS at 20 Hz significantly increased global blood flow, whereas rTMS at 1 Hz did not.[20] Lefaucheur et al.[7] evaluated the effect of rTMS at two frequencies (10 and 0.5 Hz) in 18 patients with intractable unilateral hand pain. The VAS score improved in response to 10-Hz stimulation but did not improve in response to 0.5-Hz stimulation. In addition, good pain control has been reported in response to high-frequency stimulation (10 or 20 Hz) in some rTMS studies.[13,22] Effectiveness of low-frequency (1-Hz) rTMS was reported only in healthy individuals with acute pain caused by capsaicin.[21] The findings are consistent with our results indicating that 5- and 10-Hz rTMS are effective but 1-Hz rTMS is not.

It is likely that the greater the stimulation frequency, the greater the effect of rTMS on pain reduction. Lefaucheur et al.[8] used 80% of the resting motor threshold of the intact hand for rTMS treatment of deafferentation pain. We used 90% of the resting motor threshold of the affected limb, and our rTMS was of higher power than theirs. Our success rate seemed to be superior to theirs. However, suprathreshold rTMS of the precentral gyrus corresponding to the affected limb and stimulation at frequencies of greater than 10 Hz appear to increase the risk of seizure development in patients who have suffered stroke. Therefore, we did not evaluate these types of rTMS. In the future, subthreshold rTMS with 5 or 10 Hz may prove to be useful for clinical applications of rTMS.

We believe that it is very difficult to apply all rTMSs to the same cortical area. We therefore performed rTMS using a frameless magnetic resonance imaging–guided navigation system in accordance with each patient's own cortical anatomy. The TMS coil was positioned by an articulated coil holder. Without a navigation system, identification of the precentral gyrus is difficult in patients with severe motor weakness whose motor evoked response is barely induced by a single TMS. The anatomical error of the navigation system is considered to be less than about 5 mm. This is based on the observation that muscle twitches did not occur if the coil was out of position by about 1 cm on the magnetic resonance imaging–guided navigation system. Experimental simulation showed that the electrical current induced with the figure-eight coil is considerably limited in the cortex. We consider a navigation system to be indispensable when performing rTMS.

We have reported that there is good correlation between the results of rTMS and those of MCS.[15] Migita et al.[10] reported on two patients with central pain who were evaluated using rTMS of precentral gyrus and then treated using MCS. We believe that high-frequency rTMS can predict the results of MCS.

Conclusions

Subthreshold high-frequency rTMS of the precentral gyrus significantly reduces intractable pain for up to 180 minutes. Low-frequency rTMS is ineffective. Treatment with the aid of rTMS appears to be more effective in patients with a spinal cord or peripheral lesion than in those with a cerebral lesion. Several brain regions associated with pain perception may be activated by subthreshold high-frequency rTMS of the precentral gyrus, and such stimulation may reduce deafferentation pain comprehensively. The rTMS may be a good predictor of MCS efficacy, and thus, we believe that MCS can be recommended to patients who have good results from rTMS.

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Short-term Preoperative Octreotide Treatment of GH-secreting Pituitary Adenoma: Predictors of Tumor Shrinkage

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Abstract. We reviewed the cases of 32 patients with growth hormone (GH)-secreting macroadenoma who underwent short-term octreotide treatment before transsphenoidal surgery to determine which types of adenoma the preoperative treatment were sensitive and whether predictors of tumor shrinkage could be identified. The effects of preoperative octreotide treatment, endocrinologic effect and effect on tumor volume in 32 patients were evaluated retrospectively in relation to tumor features on magnetic resonance images and responses to endocrinologic challenge tests. At a daily dose of 300 μg for 2–3 weeks, octreotide reduced serum GH and insulin-like growth factor-1 (IGF-1) levels to 31.9 % and 51.6% of pretreatment values, respectively, and led to a mean tumor volume of 68% of pretreatment volume in 52% of the patients. The endocrinologic effect and the effect on tumor volume were larger in Knosp grades 0–2 than in Knosp grades 3–4. Tumor shrinkage occurred significantly more often among patients that had a good response to both octreotide and bromocriptine challenge tests. For surgical removal of the tumor, the effect of reducing tumor to 68% of pretreatment volume will be beneficial for the macroadenomas of Knosp grades 1–2. Preoperative short-term octreotide treatment is effective for GH-secreting macroadeomas of Knosp grades 1–2 and a good response to both octreotide and bromocriptine challenge tests is a predictor of subsequent tumor shrinkage. These results will lead to more effective selection of patients for preoperative octreotide treatment.

Key words: Acromegaly, Octreotide, Bromocriptine, Tumor shrinkage

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ACROMEGALY is an insidious disorder caused by GH-secreting pituitary adenoma and resulting in high circulating serum GH and insulin-like growth factor-1 (IGF-1) levels [1]. It is widely accepted that GH-secreting adenoma requires multimodal treatment, for example, surgery, radiation (radiosurgery), and medical treatment with somatostatin analogues (*e.g.* octreotide) and dopamine agonists. Even with the development of medical treatment and radiosurgery, transsphenoidal surgery is still widely accepted as the first choice treatment [2].

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According to new remission criteria for acromegaly (Cortina consensus) [3], 80–90% of patients with GH-secreting microadenoma and 40–65% of those with macroadenomas are controlled by transsphenoidal surgery alone at the experienced centers [2, 4–7]. Tumor size and degree of invasion into the cavernous sinus are critical factors for the outcome of transsphenoidal surgery [8]. Improving the surgical remission rate of GH-secreting macroadenomas is an important objective for pituitary neurosurgeons.

Octreotide decreases serum GH and IGF-1 levels and reduces the size of the GH-secreting adenoma in some patients, and it has been widely used postoperatively in patients without surgical remission. Octreotide has also been applied preoperatively in the hope of favorable effects on the surgical outcome. Several reports have shown the benefits of preoperative oct-