1. Introduction

In slowly progressive brain tumors, impairment of motor function does not become apparent until a certain area of motor cortex or subcortical fibers is involved. Clinical observations of patients suggest that functional remodeling with neurophysiological dysfunction in the brain is taking place during the gradual growth of the tumor. For surgical treatment of tumors involving the motor areas, elucidation of this dysfunction or remodeling is important for pre-surgical planning and for effective rehabilitation.

The cerebral cortex including motor cortex exhibits oscillatory rhythms at rest [1], which can be modulated by pathological states as well as functional activation [2,3]. A recently developed synthetic aperture magnetometry (SAM) has been proved useful to estimate the tomographic distribution of the intensity of electrical activity within a selected band frequency, and its statistical derivatives from unaveraged MEG signal [4].

In this study, we applied SAM to evaluate the possible relation between the topographic distribution of focal slow-wave activity recorded by spontaneous MEG and the clinical symptoms and to study the power decrease in background brain activity during a motor task (event related desynchronization, ERD) in patients with brain tumors around the central sulcus.

2. Methods

Eighteen patients with brain tumors around the central sulcus and four control subjects were studied. Among them, 12 patients were evaluated on focal oscillatory activity (delta, theta and alpha bands) from the spontaneous MEG.

The areas displayed in SAM pZ image were assigned to four groups based on their locations in relation to the tumor: AC, adjacent to the tumor; EC, area lying over subcortical edema; IC, cortex ipsilateral to the tumor; and CC, cortex in the contralateral hemisphere. To assess whether the areas with high peak pZ values were located around the tumor, their peak pZ values in AC, EC and IC were compared with those for CC by the non-parametric Mann–Whitney U-test. Since the coverage of current source in the cortex by the sensor array was almost equivalent for each region of interest, we assumed pseudo-Z values could be comparable each other.

The rest of the patients ($N=6$) were examined on the motor evoked ERD. Subjects were instructed to undertake a trial consisting of six sessions of repetitive hand grasping of either hand for 10 s after 10 s of rest, keeping their eyes closed. The beginning and end of the movement was signaled to the subject by the investigator. The MEG data were acquired on trigger at the very end of the 10 s of grasping. Volumetric images of root mean squared source activity in each frequency band were generated by SAM method from the MEG data sampled before and after the trigger as control and active states, respectively. The statistical imaging is computed subsequently by comparing the power of both states on a single voxel basis using the Student t test. Only voxels displaying peak signal changes within each trial are collected. Images with a peak t value less than 2.5 or ERD distributed evenly over the hemisphere were excluded [2,3].

3. Results

In the normal subjects, consistent ERD in the sensorimotor cortex (MI/SI) contralateral to the hand movement was observed in the beta band. Those ERD were almost congruent

with hand representative area. Additional beta ERD was observed on the ipsilateral superior parietal lobule during dominant hand movement ($N=1$) and on the ipsilateral MI/SI ($N=2$), the contralateral inferior parietal lobule ($N=1$), and the superior parietal lobule and frontal operculum ($N=1$) during non-dominant hand movement. Low gamma ERD was observed in the contralateral MI/SI during dominant and non-dominant hand movement ($N=3$). In contrast, alpha ERD was observed over diverse regions of both cerebral hemispheres.

In the delta band, the statistical SAM pZ images clearly localized tumor-related focal oscillatory slow-wave activities to AC and/or EC, but not within the tumor in 11 of the 12 patients. The possible dysfunction at the identified locations was compatible with the main symptoms. Volumetric evaluation of this delta activity in AC and EC revealed that intensive were far more prominent in patients with intra-axial tumors, compared with those with extra-axial tumors. Enhanced delta activity within a large volume of cortex was noted around M1/S1 in the patients with poor functional outcome post-operatively.

In the theta band, the enhanced power observed in AC or EC was distributed more diffusely than in the delta band. In the alpha band, the power source was distributed bilaterally around the primary sensorimotor cortex. No consistent findings were obtained with respect to tumor location or presenting signs and symptoms.

For hand movement on the non-affected side, the beta ERD was observed on contralateral MI/SI and in the inferior parietal lobule (three and four subjects, respectively). For hand movement on the affected side the beta ERD was observed on ipsilateral MI/SI lateral to the assumed hand representative area ($N=4$), in the lateral pre-motor area ($N=2$), and in the inferior parietal lobule ($N=1$).

The low gamma ERD was observed in the contralateral MI/SI ($N=2$) and the pre-motor area during non-affected hand movement ($N=2$) and in the ipsilateral MI/SI during affected hand movement ($N=3$). The alpha ERD was observed in diverse regions without any strong consistency.

4. Discussion

In this present study, SAM analysis based on spontaneous MEG in patients with symptomatic brain tumors around the central sulcus revealed the presence of localized sources of delta-band activity in regions which corresponded to the presenting signs and symptoms in 11 of the 12 patients. Because the areas selected as "sources" consistently exhibited the highest delta activity they are likely to represent the most severely damaged regions. Therefore the positive correlation between the enhanced delta activity and the clinical symptoms indicates that the former represents a truly dysfunctional state. In fact, the distribution of areas with enhanced delta activities was heterogeneous within AC or EC, especially in patients with meningiomas. This indicates that the damage to surrounding tissues inflicted by tumors is highly variable and this may cause differences in clinical pictures.

Furthermore, patients with intra-axial tumors who manifested prominent subcortical edema and presented with more severe neurological symptoms and poorer surgical outcome, had a larger number of voxels with enhanced delta-band activity than patients with extra-axial tumors such as meningioma. It suggests that subcortical fibers, including thalamocortical fibers, are more impaired in patients with intra-axial tumors, which results in more prominent neurological deficits and emergence of enhanced delta-band activity.

These findings may indicate the difference in generators of tumor related slow-wave activity between intra-axial and extra-axial tumors [3].

The most prominent finding in motor evoked ERD study was the lack of beta ERD in the MI/SI contralateral to the hand movement on the affected side in the patients. This does not necessarily mean a lack of activity in the MI/SI, as ERD is a reflection of the modulation on basic rhythm by a motor event. Thus if the basic rhythm were suppressed in the resting state owing to the presence of the tumour and the surrounding edema, the ERD would not become apparent.

The beta band power attenuation in sensors on the affected side in the resting state, in comparison with the non-affected side, would provide evidence for the basic rhythm alteration in the tumour bearing hemisphere, making the above mentioned hypothesis plausible. Nevertheless, the ipsilateral ERD during affected hand movement would suggest that considerable mobilization of the ipsilateral motor areas is mandatory to maintain appropriate motor function [2]. This suggests that the affected motor cortex does not function fully in the normal range even at the stage when the motor impairment is not apparent at all, as was the case in most of the patients studied. The application of diffusion tensor imaging would be further step to study the influence of cortical and subcortical involvement to the lack of beta ERD in the affected motor areas and increased delta activity.

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Motor cortex stimulation in patients with deafferentation pain: activation of the posterior insula and thalamus

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Object. The mechanisms underlying deafferentation pain are not well understood. Motor cortex stimulation (MCS) is useful in the treatment of this kind of chronic pain, but the detailed mechanisms underlying its effects are unknown.

Methods. Six patients with intractable deafferentation pain in the left hand were included in this study. All were right-handed and had a subdural electrode placed over the right precentral gyrus. The pain was associated with brainstem injury in one patient, cervical spine injury in one patient, thalamic hemorrhage in one patient, and brachial plexus avulsion in three patients. Treatment with MCS reduced pain; visual analog scale (VAS) values for pain were 82 ± 20 before MCS and 39 ± 20 after MCS (mean ± standard error). Regional cerebral blood flow (rCBF) was measured by positron emission tomography with $H_2{}^{15}O$ before and after MCS. The obtained images were analyzed with statistical parametric mapping software (SPM99).

Results. Significant rCBF increases were identified after MCS in the left posterior thalamus and left insula. In the early post-MCS phase, the left posterior insula and right orbitofrontal cortex showed significant rCBF increases, and the right precentral gyrus showed an rCBF decrease. In the late post-MCS phase, a significant rCBF increase was detected in the left caudal part of the anterior cingulate cortex (ACC).

Conclusions. These results suggest that MCS modulates the pathways from the posterior insula and orbitofrontal cortex to the posterior thalamus to upregulate the pain threshold and pathways from the posterior insula to the caudal ACC to control emotional perception. This modulation results in decreased VAS scores for deafferentation pain.
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KEY WORDS • **deafferentation pain** • **motor cortex stimulation** • **posterior insula** • **posterior thalamus** • **regional cerebral blood flow**

DEAFFERENTATION pain is the most difficult type of pain to treat. Tsubokawa et al.[38] developed the use of MCS. Katayama et al.[14] reported that the use of MCS provided pain relief in approximately 50% of patients with thalamic pain. Meyerson[19] and Nguyen[21,22] and their colleagues showed that facial deafferentation pain was decreased by MCS. Son et al.[34] reported the effectiveness of MCS on complex regional pain syndrome Type II. We also reported that MCS is effective for treating peripheral and spinal cord deafferentation pain (brachial plexus injuries, phantom limb pain, and spinal cord injuries).[30]

Recent advances in functional imaging and neurophysiological methods have made it possible to examine neuronal activity in response to various tasks. Cerebral responses to peripheral pain have also been studied by many investigators in animal models of acute pain and in normal volunteers undergoing thermal, laser, or chemical stimulation.[12,17,18,20,24,33,42] Because animal models of chronic pain are difficult to carry out, few studies have focused on the mechanisms of chronic intractable pain,[28] although authors have speculated on the mechanisms on the basis of clinical results. The mechanism of MCS in the treatment of post-stroke pain was addressed by Tsubokawa et al.[39] They speculated that fourth-order nonnociceptive neurons are activated by MCS and inhibit hyperactive nociceptive neurons. It has also been reported that the anterior thalamus, brainstem, cingulate gyrus, and orbitofrontal cortex are activated during MCS.[10,25] The somatosensory cortex is not activated by MCS. Motor cortex stimulation may influence the affective-emotional component of chronic pain, and inhibitory control of pain involves thalamic and brainstem relays to descending pathways down to spinal cord segments, resulting in the attenuation of spinal flexion reflexes. The results of our preliminary PET study showed that the contralateral posterior thalamus was activated after treatment with right MCS for thalamic pain.[29]

Abbreviations used in this paper: ACC = anterior cingulate cortex; BA = Brodmann area; ICBM = International Consortium for Brain Mapping; FWHM = full width at half maximum; MCS = motor cortex stimulation; M1 = primary motor cortex; PET = positron emission tomography; rCBF = regional cerebral blood flow; SPM = statistical parametric mapping; VAS = visual analog scale.

In the present study, we used $H_2{}^{15}O$ PET to investigate the pattern of MCS-related neuronal activation and/or attenuation before and after MCS; $H_2{}^{15}O$ PET shows rCBF, which reflects focal neuronal activation.[13] We also used a recently developed method of statistical analysis involving parametric mapping of normalized brain images. Six patients with chronic deafferentation pain in the left hand and with electrodes placed on the right precentral gyrus corresponding to the M1 of the left hand were studied. This method provides more accurate results than those reported previously because the M1 is precisely and specifically stimulated.

Clinical Material and Methods

Patients and Surgical Procedure

Six right-handed patients (four men and two women, age range 50–67 years) with intractable deafferentation pain in the left hand were included in this study (Table 1). Deafferentation pain had resulted from brainstem injury (one patient), cervical spine injury (one patient), thalamic hemorrhage (one patient), and brachial plexus avulsion (three patients). The patients had suffered from intractable pain for 3 to 27 years, and medication had been ineffective. All of the patients showed slight to moderate motor weakness in the left arm. The VAS (grading range 0–100) and the short form of the McGill Pain Questionnaire were used to evaluate the degree of pain.

The surgical procedure was performed as described previously.[29,30] In brief, the location of the central sulcus was approximated with the use of preoperative magnetic resonance images and confirmed by intraoperative phase reverse of the N20 component of the somatosensory evoked potential upon stimulation of the left median nerve,[43] recorded with an evoked potential recorder (Neuropack 8, Nihon Kohden Co. Ltd.). A 20-grid set of electrodes (4 × 5 array, 0.3-cm-diameter electrode, 0.7-cm separation; Unique Medical Co. Ltd.) was implanted subdurally, covering the convexities of the pre- and postcentral gyri of the left hemisphere. After confirmation of pain reduction in response to stimulation for 10 to 14 days, a permanent four-array stimulating electrode (Resume II, model 3587A, Medtronic, Inc.) was placed subdurally at the surface of the right precentral gyrus at the site associated with the most effective pain reduction. The electrode was controlled by a subcutaneously implanted stimulator (Itrel III, Medtronic, Inc.).

Bipolar stimulation[30] was used for pain relief, and stimulation parameters varied in each patient. The general ranges were: voltage, 0.6 to 3.5 V; frequency, 25 to 40 Hz. The pulse width was 210 microseconds, and stimulation was administered for 30 minutes one to four times a day. The patients used MCS for at least 6 months.

The PET Scanning Procedure and Activation Task

The PET study was performed 1 to 3 years after implantation of the stimulation electrode. A Headtome V PET scanner (Shimadzu Co.) was used to scan in the 3D acquisition mode with a head shield. Patients went without cortical stimulation for more than 12 hours before the PET study. The patients lay with eyes closed in a silent and dim room. A 15-minute transmission scan was performed first with ^{68}Ge sources to correct for γ-ray attenuation. Relative cerebral blood flow was measured based on the distribution of radioactivity after slow bolus intravenous injection of $H_2{}^{15}O$ (7 mCi/scan, each lasting 90 seconds). Six PET scans corresponding to six $H_2{}^{15}O$ injections were performed before MCS; MCS was performed for approximately 30 minutes; and six PET scans were performed after confirmation of pain reduction. The PET protocol was as described previously.[29]

TABLE 1

General characteristics of patients with deafferentation pain

Case No.	Age (yrs), Sex	Associated Lesion	Duration of Pain (yrs)
1	50, F	brainstem injury	3.3
2	50, F	cervical spine injury	6.0
3	59, M	thalamic hemorrhage	8.3
4	67, M	brachial plexus avulsion	27.0
5	57, M	brachial plexus avulsion	4.0
6	56, M	brachial plexus avulsion	3.0

Data Analysis

Attenuation-corrected data were reconstructed into an image (voxel sizes: 2 × 2 × 3.125 mm; field of view: 256 × 256 × 196 mm) with a resulting resolution of 4 × 4 × 5 mm at FWHM. The images were analyzed with SPM software (SPM99; Wellcome Department of Cognitive Neurology).[7] The PET images were anatomically normalized in fit with ICBM coordinates of the Montreal Neurological Institute. Images from each patient were realigned to the first volume of PET images and normalized to the template[7] to account for variation in gyral anatomy and interindividual variability in structure–function relationships, and to improve the signal-to-noise ratio. This procedure was used for image realignment, anatomical normalization, smoothing (12 mm at FWHM), and statistical analysis.[15] Data were normalized to global blood flow (average 50). The effect of state-dependent differences in global blood flow was tested with analysis of covariance.

All six patients were included in the same statistical analyses, with voxel-to-voxel comparison. Statistical parametric maps were generated with an analysis of variance model using the General Linear Model formulation of SPM99.[9] We analyzed the main effect of MCS by comparing images obtained after MCS with those obtained before MCS with the statistical threshold set at a probability value of less than 0.005 for peak height, corrected for spatial extent (> eight voxels per cluster). We also categorized post-MCS sessions as follows: the first two scans in the 20 minutes just after MCS were denoted as the early post-MCS phase and the last two scans more than 40 minutes after MCS were denoted as the late post-MCS phase. We generated SPM (t) maps of rCBF changes associated with each comparison. For between-group comparisons, the SPM (t) maps were transformed into SPM (Z) maps, and the levels of significance of areas of activation were assessed according to peak height of foci estimation based on the theory of random Gaussian fields. Significance was accepted if a cluster showed a corrected probability value of less than 0.05. Data are presented as means ± standard errors.

This study adhered to the guidelines of the Declaration of Helsinki on the use of human subjects in research, and the patients provided written informed consent.

Results

Pain Reduction in Response to MCS

After MCS, all six patients showed various degrees of pain reduction according to VAS data (from a mean of 82 ± 20 to a mean of 39 ± 20). The duration of the MCS effect differed between the patients, ranging from 2 to 12 hours. In this study, we found that the pain reduction began during MCS and continued for at least 30 minutes after MCS. The pain reduction was stable during the six post-MCS PET scans. The results of the short form of the McGill Pain Questionnaire agreed for the most part with the VAS scores.

Brain Activation Profiles in Response to MCS

Comparison of rCBF before and after MCS showed significant rCBF increases after MCS in the left posterior thalamus (pulvinar) and left posterior insula (the six cases were analyzed together, corrected cluster $p = 0.044$; Table 2, Fig. 1A and B). No areas of significant rCBF decrease were identified. When we compared the scans obtained in the early post-MCS phase with the six pre-MCS scans, we found significant rCBF increases in the left posterior insula ($p = 0.011$) and the right orbitofrontal cortex (BA 11) ($p = 0.047$) (Table 2, Fig. 1C and D). Significant decreases in rCBF were identified between the right middle frontal gyrus (BA 9) and the right precentral gyrus (BA 4) ($p = 0.048$) (Table 3, Fig. 2).

When scans obtained in the late post-MCS phase were compared with the six pre-MCS scans, the left caudal part of the ACC (BA 24) showed significant increases in rCBF ($p = 0.005$; Table 2, Fig. 1E). Comparing rCBF in the early post-MCS phase with that in the late post-MCS phase, rCBF in the left medial frontal gyrus (supplementary motor area; BA 6) was increased in the late phase ($p = 0.033$, cluster size, 309; Talairach coordinates, $x = 3$, $y = -5$, $z = 59$).

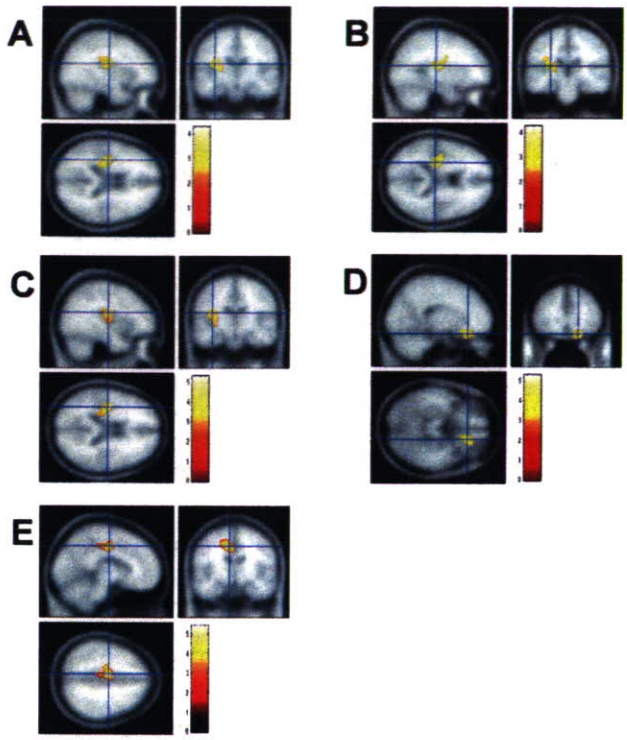

FIG. 1. Representative SPM (Z) intensity maps in normalized images. Comparison of rCBF before and after MCS showed that rCBF was increased after MCS in the left posterior insula (A) and left posterior thalamus (B). Comparison of rCBF before MCS and in the early post-MCS phase showed that rCBF was increased in the early post-MCS phase in the left posterior insula (C) and right orbitofrontal cortex (BA 11) (D). Comparison of rCBF before MCS and in the late post-MCS phase showed that rCBF was increased in the late post-MCS phase in the left ACC (E). The *colored bars* indicate the Z values; ($p < 0.005$).

Discussion

All of the right-handed patients in this study complained of left-hand pain, and the nondominant (right) precentral gyrus was stimulated electrically. Preoperative MR images and intraoperative somatosensory evoked potentials were used to determine the location of the central sulcus. Thus, we were able to precisely stimulate the area of the precentral gyrus corresponding to the left hand. We observed changes in neuronal activity with $H_2{}^{15}O$ PET, and all PET images were normalized and then analyzed using SPM.[7,8,9,15] Therefore, the results of this study were based on anatomically well-standardized samples and equal stimulation of identical brain regions.

TABLE 2

Areas of increased rCBF after MCS

Condition & Areas	Cluster		Talairach Coordinates (x, y, z in mm)	Voxel Equivalent Z
	p Value (corrected)	Size (voxel)		
pre-MCS compared w/ all phases of post-MCS				
lt insula	0.044	685	−31, −19, 15	3.57
lt thalamus			−25, −26, 11	3.38
pre-MCS compared w/ early phase of post-MCS				
lt insula	0.011	593	−33, −19, 15	4.44
rt orbitofrontal cortex (BA 11)	0.047	420	15, 26, −15	4.32
pre-MCS compared w/ late phase of post-MCS				
lt cingulate cortex (BA 24)	0.005	406	−8, −15, 38	4.47

TABLE 3
Areas of decreased rCBF after MCS

Condition & Areas	Cluster		Talairach Coordinates (x, y, z in mm)	Voxel Equivalent Z
	p Value (corrected)	Size (voxel)		
pre-MCS compared w/ early phase of post-MCS				
rt prefrontal cortex (BA 9)	0.048	406	29, 16, 29	4.10
rt precentral cortex (BA 4)			22, −11, 48	3.48

In this study, neither sham stimulation nor a control study was indicated. We used test stimulations of 10 to 14 days prior to the second surgery. Patients who had showed no effect or sham effect were excluded. And all of the patients in this study had used MCS for at least 6 months and had confirmed the effectiveness of MCS. We believe that there was no placebo effect associated with MCS in these cases.

It is not clear whether electrical stimulation activates or suppresses neurons around the point of stimulation. Some researchers have reported that low-frequency (5 Hz) stimulation of the cortex results in long-term potentiation of corticostriatal neuron activity in rats,[2] but the relationship between frequency of stimulation and effect on surrounding neurons has not been clarified. In our study, all patients showed the most pain reduction at frequencies between 25 and 40 Hz. Thus, we conclude that 25 to 40 Hz is a suitable range for MCS treatment of intractable pain. We found that stimulation in this frequency range decreased rCBF in the M1 for at least 20 minutes after MCS, indicating that the level of electrical stimulation used in this study inhibits neuronal activity under the electrode.

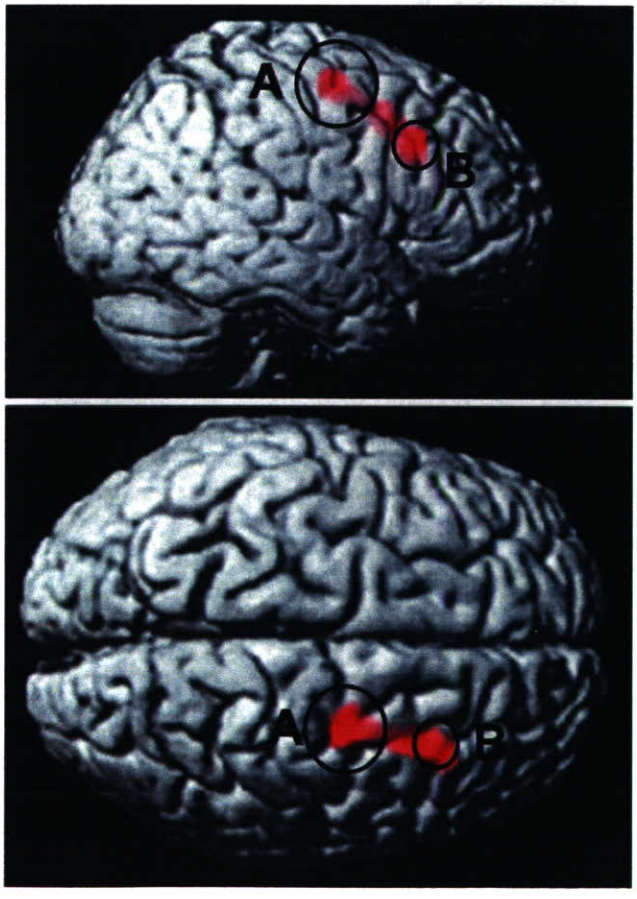

FIG. 2. Normalized images showing regions of significantly decreased rCBF in the early post-MCS phase compared to rCBF before MCS. *A* indicates the area of the precentral cortex (BA 4) and *B* the area of the dorsolateral prefrontal cortex (BA 9); ($p < 0.005$).

In this study, MCS did not alter rCBF in the postcentral gyrus (primary sensory cortex). This finding supports reports that MCS-induced pain reduction does not involve normal sensory pathways.[10,26] In fact, Drouot et al.[5] reported that MCS for control of chronic pain improves abnormal sensory thresholds. Thus, relief of chronic pain by MCS does not depend on sensory suppression and does not involve neuronal activity of the primary sensory cortex.

The rCBF in the right dorsolateral prefrontal cortex (BA 9) was also decreased after MCS. The prefrontal cortex is considered to include attentional and memory networks activated by noxious stimulation.[23,27] Lorenz et al.[18] also reported that BA 9 exerts active control of pain perception by modulating corticosubcortical and corticocortical pathways. Furthermore, repetitive transcranial magnetic stimulation of BA 9 has been reported to be effective in the treatment of depression.[6] Reduced BA 9 neuronal activity in the early post-MCS phase may reflect attenuation of attention and perception of chronic pain and may control psychological state.

The left posterior insula was activated in the early post-MCS phase. The posterior insula as well as the secondary somatosensory cortex are well described as reflecting pain perception and are parametrically activated by nociceptive input.[23,25,27,33,40] It was recently reported that in the rostral agranular insula, γ-aminobutyric acid can alter pain thresholds in rats and that locally increasing the level of this neurotransmitter in the insula induces analgesia by enhancing descending inhibition of spinal nociceptive neurons.[12] The posterior insula has connections to the periaqueductal gray matter, the area around the locus caeruleus, the rostroventral medulla, and the mesolimbic/mesocortical ventral forebrain.[11] Schlereth et al.[31] speculated that the left dorsal insula plays a dominant role in the early sensory-discriminative phase of pain processing. Thus, MCS appears to activate the left dominant posterior insula, resulting in upregulation of the pain threshold.

We found significantly increased rCBF in the right orbitofrontal cortex in the early post-MCS phase. Jasmin et al.[11] reported that the rostral agranular insula possesses reciprocal connections with the orbital infralimbic cortex and ACC in rats. It has also been reported that the cingulofrontal cortex, including the orbitofrontal cortex and the ACC in the area around the genu of the corpus callosum, exerts

a topdown influence on the posterior thalamus and periaqueductal gray matter to gate pain modulation during distraction.[40] The left posterior thalamus was activated in the early post-MCS phase in our study. Thus, it is possible that the activated orbitofrontal cortex, together with the posterior insula, excites the dominant posterior thalamus to upregulate the pain threshold.

The area of rCBF increase included the pulvinar of the thalamus (according to the atlas of Talairach and Tournoux[35]). In the 1970s, the posterior thalamus (pulvinar) was a target of lesioning surgery for cancer pain, and pulvinotomy resulted in early relief of cancer pain in most patients, but the pain often recurred.[37] Although the function of the posterior thalamus is not well characterized, we speculate that the dominant posterior thalamus is involved in chronic deafferentation pain.

Garcia-Larrea et al.[10] reported that the ipsilateral motor thalamus (ventrolateral and ventroanterior thalamus) and brainstem regions are activated by MCS. The ipsilateral thalamus shows hypometabolism in cases of central pain.[4,16] In our study, the ipsilateral (right) thalamus was not affected. In addition, one patient had poststroke pain but not severe motor dysfunction; others in this study had brainstem, spinal cord, or peripheral nerve injuries. Thus, corticostriatothalamic connections relating to movements were preserved in all patients, resulting in preserved right motor thalamus function.

The posterior insula projects efferent fibers to the amygdala in rats.[11] The bilateral caudal ACC and the posterior insula/secondary somatosensory cortex have been reported to be specific to the experience of pain.[1,33] It has also been reported that the caudal part of the right ACC is activated when the right M1 is stimulated magnetically in a capsaicin-induced pain model,[36] and the ACC is also activated by thalamic stimulation in patients with chronic pain.[3] The amygdala and cingulate gyrus belong to the limbic system and play important roles in emotional control. The caudal ACC (BA 24) contains the cingulate motor area,[32] which is associated with emotional behavior.[41] Our data showed that not only the posterior insula but also the caudal ACC (BA 24) were activated in response to MCS. Thus, MCS for treatment of chronic deafferentation pain modulates pain-related emotion and mood, resulting in pain relief. The caudal ACC, which was activated in the late post-MCS phase, contributes to long-lasting pain relief (several hours of relief) induced by MCS.

Conclusions

The use of MCS for the treatment of deafferentation upregulates the pain threshold by modulating pathways from the posterior insular and orbitofrontal cortex to the posterior thalamus. Treatment with MCS also controls pain-related emotion by modulating the pathway from the posterior insula to the caudal ACC. These findings support the use of MCS for treatment of deafferentation pain.

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Genetics

Immunohistochemical detection of female sex hormone receptors in craniopharyngiomas: correlation with clinical and histologic features

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Abstract

Background: Although craniopharyngiomas have a histologically benign nature, their treatment can be difficult. The correlation among clinical, proliferative, and immunohistologic features of female sex hormone receptors was determined in craniopharyngiomas to analyze whether they influence the growth of the tumor.

Methods: The study subjects were 43 patients with previously untreated craniopharyngioma who underwent surgery at our department over the past 15 years. Serial tissue sections were immunostained with the antibodies against estrogen receptor (ER), progesterone receptor (PR), and Ki-67.

Results: The Ki-67 labeling index was significantly higher in patients with regrowth (7.8%) than without regrowth (3.9%). ER and PR were detected in 9 of 30 (30%) craniopharyngiomas, and the incidence of postoperative tumor regrowth was significantly higher in patients negative for ER and PR (29%) than in those positive for both receptors (11%).

Conclusions: A high Ki-67 labeling index suggests a high possibility of tumor regrowth, and the presence of ER and PR is suggestive of a high tissue differentiating potential. ER and PR assay may be useful for determining the indication for additional radiation therapy in craniopharyngioma patients treated by incomplete resection.

Keywords: Craniopharyngioma; Estrogen receptor; Ki-67; MIB-1; Progesterone receptor

1. Introduction

Craniopharyngiomas are benign central nervous system tumors thought to derive from ectopic remnants of the pharyngeal epithelium following the embryologic evagination of Rathke's pouch [1]. Despite their histologically benign nature, their treatment can be difficult. Whereas total resection is the basic surgical approach, especially in young patients, aggressive surgery is associated with high risk [11,17,22]. Even in patients with apparent gross total resection, the recurrence rate at 10 years is about 19% [5,21]. As patients with subtotal or partial resection have a high incidence of tumor regrowth, combined radiotherapy has been recommended [18]. In cases where it is difficult to confirm total resection and in patients with residual tumors, decisions must be made regarding postoperative monitoring in the absence of further treatment or whether conventional radiotherapy or stereotactic radiosurgery should be performed immediately.

To settle the controversy whether a high Ki-67 labeling index is a useful predictor of craniopharyngioma, regrowth, or recurrence [6,15,16], an understanding of the molecular mechanisms underlying craniopharyngioma growth is needed. This knowledge would also be useful for developing therapeutic strategies to treat craniopharyngiomas. Sex hormones are reportedly involved in the biologic activity of tumor cells in patients with craniopharyngioma [12,20]

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and the size of some craniopharyngiomas increased following pregnancy [14]. The expression of sex hormone genes by the proliferative epithelial elements of these tumors raises the question of a possible hormonal component in the genesis and/or progression of craniopharyngiomas. Estrogens play a physiologic role in the genesis and treatment of breast cancer, and they are known to modulate neoplastic growth. Their effects are mediated by specific estrogen receptors (ER) that behave as nuclear transcription factors that induce the expression of key regulatory genes [7,9,10]. Progesterone receptor (PR)–negative meningiomas tend to be larger than PR-positive tumors, and the PR status of meningiomas is related to the differentiation of the tumor and may be of prognostic value with respect to its biologic behavior [2]. However, the biologic function(s) of sex hormones in craniopharyngiomas and their molecular basis remains unknown. In contrast to other central nervous system tumors, controversy continues to surround the importance of histopathologic analysis as a predictor of recurrence and clinical outcomes in patients with craniopharyngioma [8,16].

As hormonal factors may influence the growth of craniopharyngiomas, we immunohistochemically investigated the presence and cellular distribution of ER and PR and evaluated the relationship among receptor content and other tumor parameters such as the histologic type of the tumor and the Ki-67 labeling index.

2. Subjects and methods

The study subjects were 43 patients with previously untreated craniopharyngioma who underwent surgery at our department over the past 15 years. There were 24 males and 19 females, their age ranged from 3 to 78 years, and the tumor diameter ranged from 2 to 13 cm. Rather than attempting total resection in elderly patients with residual tumors, we combined surgical resection with postoperative radiotherapy (eg, rotating irradiation or gamma-knife therapy). Therefore, 16 of the 43 patients underwent total resection as the first therapy and the other 27 received subtotal or partial resection.

Surgical specimens from 30 patients were fixed in formalin and embedded with paraffin; hematoxylin and eosin–stained specimens were rechecked to determine the histologic tumor type. Multiple serials were subjected to immunohistochemical analysis to determine local staining. Furthermore, tissue sections were subjected to 5-minute microwave heating to activate antigens in a retrieval solution composed of 0.1 mol/L sodium citrate (pH 6) [19]. This was followed by immunostaining of the specimens by the streptavidin-biotin-peroxidase complex method [13] (Vectastain, Vector Laboratories, Burlingame, CA). We used human monoclonal antibodies against Ki-67 (MIB-1, dilution 1:20, Immunotech, Marseilles, France) and against ER and PR (1D5 and PgR636, respectively, dilution 1:100, DAKO, Carpinteria, CA). Positive immunostaining was demonstrated with the diaminobenzidine reaction, and slides were subsequently counterstained with hematoxylin, dehydrated, cleared, and mounted. The patients were divided into groups according to the extent of resection during the first operation and based on tumor regrowth after the first surgical treatment. The groups were compared with respect to histologic tumor type, Ki-67 labeling index, and positive responses to ER and PR.

3. Results

The 43 patients were followed for varying periods after the first treatment (33-183 months). Tumor recurrence or regrowth occurred in 3 of 16 patients who underwent total resection and 12 of 27 patients treated by nontotal resection. Of the latter 27 patients, 10 did not receive postoperative radiotherapy; 6 of them manifested tumor regrowth. Of the other 17 patients who received radiotherapy after nontotal resection, 5 experienced tumor regrowth. The histologic tumor type had no effect on the recurrence rate.

Magnetic resonance imaging of a 5-year-old girl (Fig. 1) disclosed a tumor and calcified lesions in the suprasellar

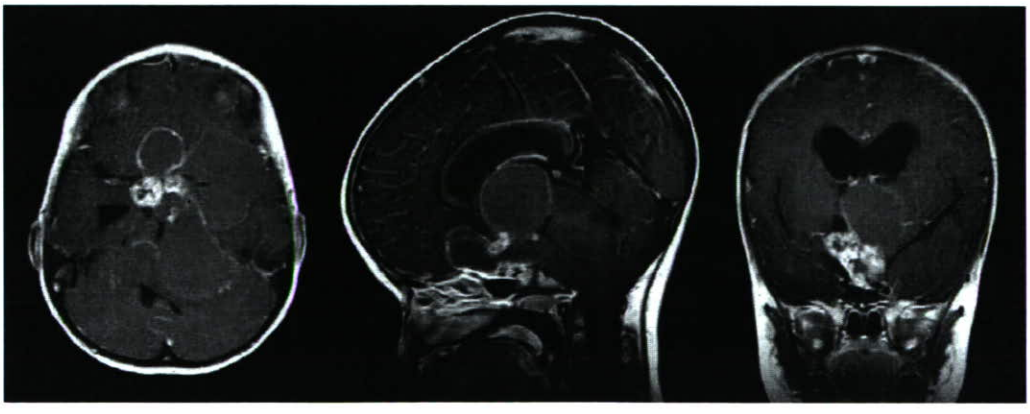

Fig. 1. Gadolinium-diethylenetriamine pentaacetic acid–enhanced T1-weighted magnetic resonance imaging obtained in a 5-year-old girl. There is a giant suprasellar cystic mass with extension to the 3rd ventricle, the middle temporal, and the posterior fossa. The solid, calcified lesion was primarily located in the suprasellar area.

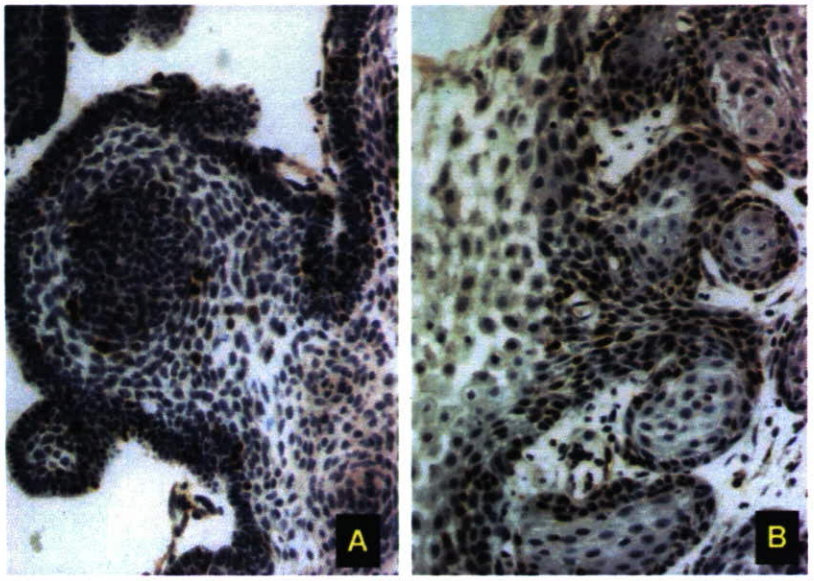

Fig. 2. Immunohistochemical staining for Ki-67. (A) The Ki-67 index was 4.8% in the 5-year-old girl shown in Fig.1. (B) The Ki-67 index was 16.89 in a 35-year-old male.

region. The tumor was a giant craniopharyngioma with a cystic component affecting extensive areas including the middle and posterior cranial fossa and the foramen magnum. There was marked adhesion in the calcified area lateral to the brainstem. A minimal tumor was left unresected in the left temporal fossa. Considering that this tumor developed in a young patient and that it was a giant tumor, we expected its growth rate to be very high. In fact, however, the Ki-67 labeling index was 4.8% (Fig. 2A), suggesting the involvement of other factors in the rapid growth of these tumors in young patients. In another patient, a 35-year-old man (Fig. 2B), the relatively small tumor was strongly attached to the optic nerve and only subtotal resection was possible. In this case, the Ki-67 labeling index was as high as 16.89%. To date, this patient has undergone 3 operations and 2 sessions of gamma-knife therapy; the size of his residual tumor has increased. This observation suggests that regrowth of this tumor after resection was not strongly correlated with patient age at onset or with the initial tumor size. Rather, biologic factors such as its cyst-forming potential and the proliferative potential of the tumor cells appear to be involved.

We subjected multiple surgical specimens from only 30 of the 43 patients to immunohistochemical investigation of ER and PR expression because the other 13 samples were too old for analysis. As shown in Fig. 3A and B, positive chromatic responses for ER and PR were confined to the nuclei; 9 of the

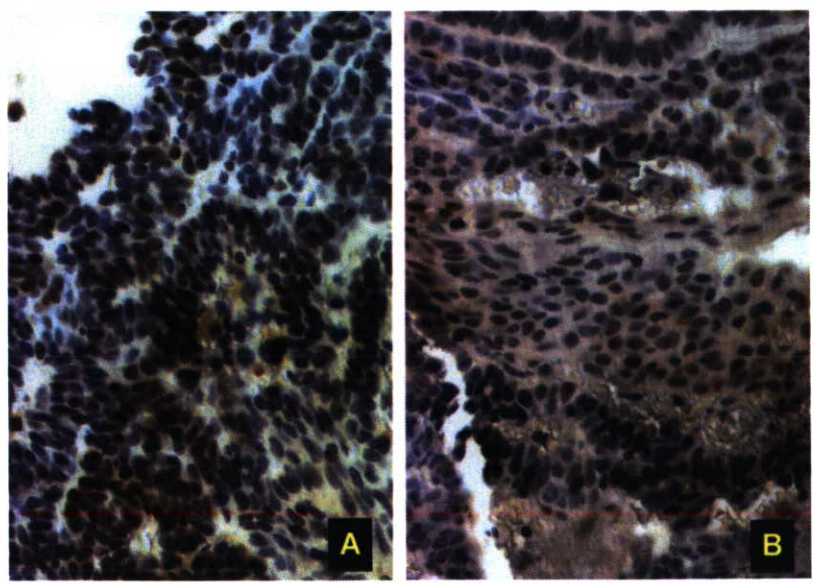

Fig. 3. Positive immunohistochemical staining for ER (A) and PR (B) in a 48-year-old male craniopharyngioma patient. There is nuclear expression of ER and PR.

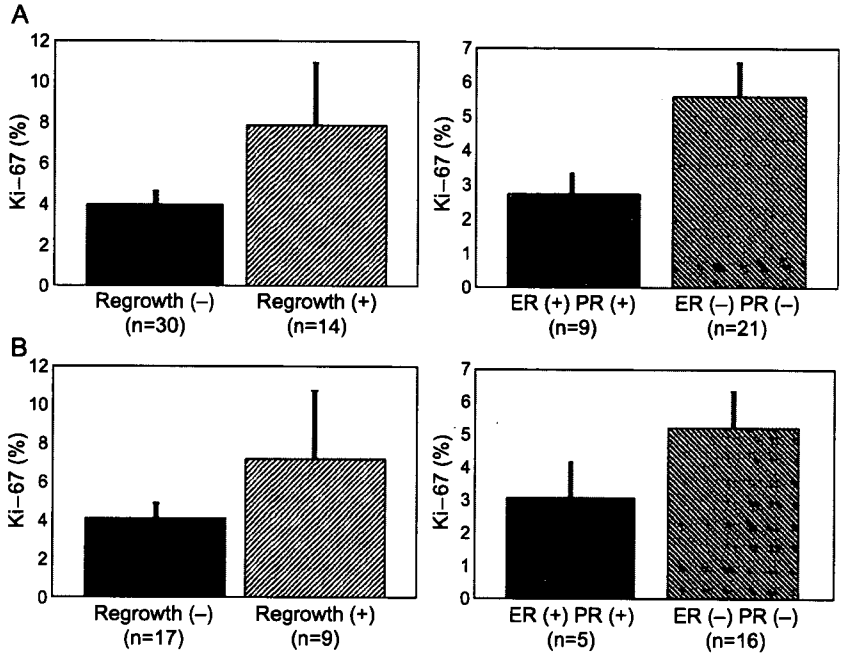

Fig. 4. (A, left) Comparison of the Ki-67 staining index (%) in craniopharyngiomas (n = 43) with or without regrowth shows that the staining index was statistically higher in cases with regrowth. (A, right) The Ki-67 index (%) in craniopharyngiomas (n = 30) was statistically higher in patients with positive immunostaining for both ER and PR. Identical analysis was carried out in craniopharyngioma patients who had not undergone radiation therapy. (B, left) Comparison of the Ki-67 staining index (%) in craniopharyngiomas who had not undergone radiation therapy (n = 26) with and without regrowth shows that the staining index was higher in cases with regrowth, but no statistical difference was obtained. (B, right) The Ki-67 index (%) in craniopharyngiomas who had not undergone radiation therapy (n = 21) was higher in patients with positive immunostaining for both ER and PR, but no statistical difference was obtained.

30 cases were positive and stained cells were detected locally in the specimens examined. We next examined the role of the Ki-67 labeling index, an indicator of the proliferative potential of tumor cells, in tumor regrowth after the initial surgical treatment. As shown in Fig. 4A, left, the Ki-67 labeling index was significantly higher in patients with than without regrowth (7.8% versus 3.9%, $P < 0.05$). In many ER- and PR-positive cases, the Ki-67 labeling index was low (average 2.7%), whereas in negative cases it averaged 5.5% (Fig. 4A, right). As shown in Table 1A, only 1 of 9 (11.1%) ER- and PR-positive patients experienced tumor regrowth after the initial surgical treatment. On the other hand, 6 of 21 (28.6%) ER- and PR-negative tumors re-grew. Based on these observations, we suggest that the detection of ER and PR in craniopharyngioma tissue reflects a high potential for tumor tissue differentiation.

Table 1
Regrowth of craniopharyngiomas and immunohistochemical results for ER and PR

	ER(+)PR(+)	ER(−)PR(−)	Total
(A) Craniopharyngiomas (n = 30)			
Regrowth (−)	8	15	23
Regrowth (+)	1	6	7
Total	9	21	30
(B) Craniopharyngiomas without radiation therapy (n = 20)			
Regrowth (−)	5	10	15
Regrowth (+)	0	5	5
Total	5	15	20

Because we expected that radiation treatment altered the biologic activity of tumor cells and thus suppressed tumor regrowth, we separately examined patients who had not received postoperative radiotherapy (Fig. 4B; Table 1B). As shown in Fig. 4B, left, we found that the Ki-67 labeling index was 4.1% in patients with tumor regrowth and 7.1% in those without tumor regrowth. As in patients not treated by radiotherapy, it was lower in the ER- and PR-positive group (3.0%) than the ER- and PR-negative group (5.1%). However, because the study population was small, the intergroup difference was not statistically significant. As shown in Table 1B, none of the 5 ER- and PR-positive, radiotherapy-treated patients manifested tumor regrowth.

4. Discussion

To determine the likelihood of recurrence and the prognosis of patients with craniopharyngioma, the histologic tumor type has been considered an important factor [1,3,4,21] and adamantinomatous tumors were thought to grow more rapidly and yield less favorable clinical outcomes than squamous tumors. However, Weiner et al [21] found that the incidence of recurrence correlated more closely with the extent of tumor resection than its histology. Radiotherapy is reportedly effective in the postoperative treatment of craniopharyngiomas [5]. Nishi et al [15], who subjected 17 craniopharyngiomas to immunohistochemical analysis of MIB-1, reported that the incidence of tumor recurrence was markedly increased in cases with a MIB-1 labeling index

exceeding 7%. They suggested that this index can serve as an indicator for the necessity of postoperative radiotherapy or chemotherapy. Our results and those of others [6] coincide with their findings. On the other hand, as cells labeled with MIB-1 are confined to a small area in tissue specimens, it is difficult to evaluate the MIB-1 labeling index and we do not consider it a satisfactory indicator.

Therefore, as hormones or hormone receptors are expressed in many types of neoplasm, we examined their role as prognostic indicators. The expression of sex hormones in meningioma has been documented [2]. In situ hybridization studies revealed that the ER gene is expressed in craniopharyngioma and PR mRNA expression was detected in cultured craniopharyngioma cells, although immunohistochemical analysis failed to detect significant amounts of ER and PR [12,20]. Although the biologic activity of ER and PR in craniopharyngioma remained unclear, they were expressed in male and female patients with this tumor. We postulate that the activation of ER and PR in craniopharyngioma cells is mediated by peptide factors and that the local tissue E2 level affects ER in an autocrine manner. Although ER may be involved indirectly in the regulation of tumor cell proliferation [20], it is difficult to confirm its expression by immunohistochemical methods, and the ER-positive rate is low on immunostained samples. Therefore, we incorporated additional processes such as antigen activation and performed our investigation across serial tissue sections because ER is often expressed locally. We found that 30% of our craniopharyngiomas expressed both ER and PR. Through analyzing the clinical course of individual cases in relation to the presence or absence of tumor regrowth, we found that detection of ER and PR suggests high differentiating potentials of tissue. We found that, irrespective of postoperative radiotherapy, patients whose tumors expressed both ER and PR had a lower rate of tumor regrowth than did patients who were negative for both ER and PR. Due to their characteristic growth patterns, it is often difficult to resect craniopharyngiomas totally, and long-term postoperative follow-up is essential [5]. In ER- and PR-positive patients with a low Ki-67 labeling index, the tumor seems to have a high differentiating potential and can be followed temporarily without additional treatment even if the craniopharyngioma was incompletely resected. Assay of ER and PR expression may provide a useful tool for determining the indication for additional radiation therapy in patients with incomplete craniopharyngioma resection.

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Commentary

This article is an interesting and provocative evaluation of the role of Ki-67 labeling index and the presence of ER and PR in craniopharyngioma recurrence and suggests that the labeling index is higher in patients with tumor regrowth and, interestingly, that the absence of the hormone receptors was also predictive of recurrence. The data are provocative but incomplete, however.

The readers will want to know how the data stratified according to age groups and also what the data were in the 16 patients with "complete resection" versus those with incomplete resection and radiation. I believe this article will probably stimulate others to attempt to replicate the results in these various subgroups and to look at this issue more closely. This is a topic that our group has had a long-standing interest in; we reported a patient with the development of a de novo craniopharyngioma who had negative ER in an article referenced by the authors [1].

Reference

[1] Magge SN, Brunt M, Scott RM. Craniopharyngioma presenting during pregnancy 4 years after a normal magnetic resonance imaging scan: case report. Neurosurgery 2001;49:1014-7.

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In the above-mentioned article, a total of 43 patients were examined. An immunohistochemical positive chromatic response for ER and PR bound to the nuclei were detected in 9 of 30 cases. Patients showing expression for these receptors were found to develop significantly higher levels of tumor regrowth. Ki-67 labeling index was also significantly higher in patients with regrowth.

According to the technical procedure of the study, it remains unclear how quantification of ER- and PR-positive cells was performed. Furthermore, correlation between positive and negative receptor expression and radiotherapy remains unclear with respect to its mechanism. It is suspected that the tumor that underwent radiation will show less regrowth.

A collective body of 43 patients seems to be very small.

ER and PR expression in craniopharyngiomas was studied in 1997 by Honegger et al [1]. In conclusion, it is important to perform further studies referring to the developing mechanism of craniopharyngiomas with respect to ER and PR transmitted mechanism.

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Editor's Choice

(Editor's Choice represents papers that the Editor found of interest that may be equally interesting to other neurosurgeons.)

Hoefgen et al (in Biol Psychiatry 57: 247–251, 2005) reported in a large homogeneous sample that the serotonin transporter gene with a genetic variant of a shorter form of the gene was significantly more frequent in patients with a Major Depressive Disorder. The transporter gene is responsible for the activity of the transporter at the membrane to take up serotonin at the synapse. When patients have the shorter form of the gene serotonin is not taken up from the synapse quickly. The result of the prolonged serotonin activity was to produce depression and related personality traits.

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Stimulation of primary motor cortex for intractable deafferentation pain

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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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Open Radiofrequency Ablation for the Management of Intractable Epilepsy Associated with Sessile Hypothalamic Hamartoma

Abstract

Sessile hypothalamic hamartoma (HH) often causes intractable epilepsy, which is difficult to control even by microsurgical resection and gamma knife surgery (GKS), especially when the hamartoma is intrahypothalamic, large, or irregularly shaped. We successfully applied radiofrequency ablation (RFA) to reduce its epileptogenicity and to disconnect seizure propagation. The patient was a 26-year-old man who presented with refractory epilepsy and severe mental retardation from age 6 months. He had undergone three surgeries yielding partial resection and conventional irradiation treatments. The residual HH was thin and shaped like a bent plate, attached widely to the floor of the third ventricle. He underwent open RFA via the transcallosal subchoroidal approach under strict image guidance, which resulted in immediate and remarkable seizure remission without complications. This suggests that open RFA is a minimally invasive technique for an irregularly shaped HH that is difficult to treat by other modalities.

Key words

Hypothalamic hamartoma · intractable epilepsy · radiofrequency ablation

Introduction

Hypothalamic hamartoma (HH) is a deep-seated congenital lesion often associated with refractory epilepsy, increased aggressiveness and precocious puberty. Previous studies indicated that HH is intrinsically epileptogenic [1] and that seizures spread through neuronal connections between the HH and the limbic system [2–4]. Total resection of the HH is recommended [5,6]; however, in many cases of intrahypothalamic or sessile HH [2], this resulted in considerable complications [6]. Gamma knife surgery (GKS) for a large HH has not been satisfactory yet [7,8]. We recently applied volumetric radiofrequency ablation (RFA) under stereotaxy for a sessile HH and successfully managed the intractable epilepsy [9]. Extending this less invasive modality to the HH in which the stereotactic technique was difficult to apply due to previous intervention, we combined preoperative image-based planning and neuronavigation with RFA under craniotomy.

Case Report

A 26-year-old man presented with a history of intractable seizures and mental retardation from the age of 6 months. The attacks were characterized by upward rotation of the eyeballs and tonic seizures, which were not controlled by any anticonvulsant. At age 2, he was diagnosed with HH and underwent three surgeries to remove the mass, resulting in partial resection. However, the frequency and intensity of the seizures were unchanged, even with radiotherapy.

Preoperatively, the patient presented with three types of seizures: gelastic seizures lasting 3 to 5 minutes (2–3/day), falling attacks (1–2/day), and generalized tonic-clonic seizures (1/day). Neurological examination showed severe mental retardation, which did not allow quantitative assessment. Magnetic resonance (MR) imaging revealed a residual mass, the inferior part

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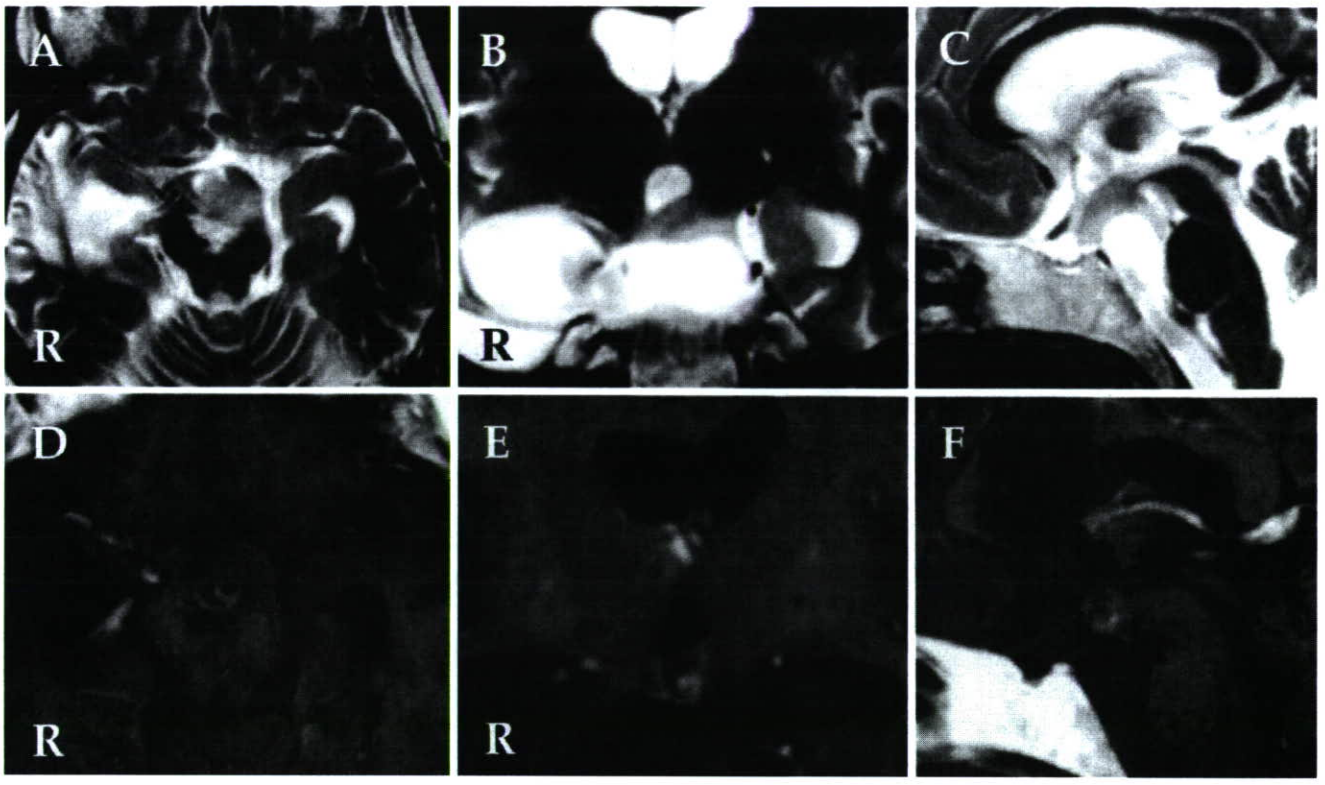

Fig. 1 Preoperative T_2-weighted MR images (**A** axial, **B** coronal, **C** sagittal) show a hypothalamic hamartoma (HH) shaped like a bent plate. Postoperative gadolinium-enhanced MR images (**D** axial, **E** coronal, **F** sagittal) show an enhanced lesion just beneath the floor of the third ventricle within the posterior part of the HH.

of which had been resected in the previous surgeries. It was shaped like a thin bent plate and attached widely to the floor of the third ventricle (Figs. **1A–C**). A contusional surgical scar appeared in the anterior part of the right temporal lobe. Single photon emission tomography showed a hot spot in the right frontotemporal area, and an interictal electroencephalogram showed spike-and-wave complexes and polyspikes predominantly in the same area.

GKS was not indicated because of potential injury to the optic pathways. Stereotactic RFA was also deemed risky because the electrode tip would not be placed properly inside of such a thin plate-like HH and injury to the perforating arteries is possible. Thus, we alternatively attempted to apply RFA directly to the floor of the third ventricle under craniotomy. Three-dimensional reconstruction of the third ventricle floor disclosed the bulge of the HH and notches between the floor and lateral walls (Figs. **2A** and **2B**), which were taken as natural landmarks during operation. An electrode penetration depth of 3 mm from the floor was chosen to accommodate the thickness of the HH, and the notches were assumed as representing the lateral borders. The third ventricle was approached via the transcallosal subchoroidal route following a right frontal craniotomy. A microelectrode inserted into the lesion revealed epileptic spikes. The extent of the hamartoma was confirmed by a frameless armless neuronavigation system (CANS Navigator, Shimadzu Co., Kyoto, Japan) [10,11]. The 12 planned ablative lesions were produced in the HH by a monopolar electrode at 80 °C for 60 seconds (Fig. **2C**), as determined at preoperative simulation (Fig. **2B**). Care was taken not to ablate the anterior part of the HH excessively to reduce the risk of diabetes insipidus. After ablation, the microelectrode was again inserted into the HH, and remission of the epileptic spikes was confirmed.

During the postoperative course, neither additional neurological nor endocrinological abnormalities appeared. The frequency of the gelastic seizures decreased immediately to once a month with cessation of falling attacks and remission of the other types of seizures, but the mental retardation remained. Postoperative gadolinium-enhanced MR images obtained 8 days after the procedure revealed a ring-like enhanced lesion indicating an ablated area (Figs. **1D–F**). During the 32-month follow-up period, the patient's daily activities increased and his psychological status improved and stabilized.

Discussion

For the treatment of intractable seizures due to HH, complete resection has been attempted for seizure cessation and improvement of behavior abnormalities; however, the HH is often difficult to approach and to resect totally without perioperative complications [5,6]. GKS has been applied in some cases of HH with good results [2,7,8]. The concept underlying use of this modality is not resection of the seizure focus but reduction of the epileptogenicity. However, the appropriate dose of irradiation has not been established considering the risk of immediate and/or remote injury to surrounding critical structures, and the effect