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Alteration of regional cerebral blood flow in patients with chronic pain —Evaluation before and after epidural spinal cord stimulation—

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Background: Chronic pain is defined as intractable pain caused by abnormal pain transmission or impairment of the pain control system per se. Alteration of regional cerebral blood flow (rCBF) is known to occur under the presence of pain stimulation. Epidural spinal cord stimulation (SCS) is occasionally effective in relieving the symptom. ***Objective:*** The aim of the current study is to investigate the alteration of rCBF in baseline condition and to find the association between the rCBF change and the efficacy of SCS in chronic pain. ***Methods:*** A total of 18 patients underwent Tc-99m-HMPAO SPECT before and after SCS. Analysis with three-dimensional stereo-tactic surface projections (3D-SSP) with stereo-tactic extraction estimation (SEE) software was adopted to evaluate the rCBF. We assessed the extent score of the abnormal region in each segment (rate of the coordinates with a Z-value that exceeds three kinds of threshold value 2.0, 2.5 and 3.0 in all coordinates within a segment). According to the therapeutic response defined by visual analogue scale, we categorized patients into two groups, the good responder (GR) group (n = 12) and poor responder (PR) group (n = 6). In the analysis, we compared the extent score in the following two conditions. (1) Comparison between the PR group and normal control group under both baseline condition and after SCS. (2) Comparison between the GR group and normal control group under both baseline condition and after SCS. ***Results:*** (1) In the PR group, increased rCBF was observed in left thalamus, bilateral precuneus and bilateral cerebellum under the baseline condition. After SCS, the range of these increased rCBF areas localized but remained. Decrease of rCBF was noted in bilateral subcallosal gyrus, superior temporal gyrus (STG) and bilateral anterior cingulate gyrus (ACG). They localized after SCS, but remained. (2) In the GR group, increased rCBF areas were noted in bilateral precuneus and bilateral cerebellum under the baseline condition. After SCS, they localized in bilateral precuneus but those of bilateral cerebellum remained. Decreased rCBF area was noted in bilateral subcallosal gyrus, STG and bilateral ACG under the baseline. After SCS, they localized in bilateral subcallosal gyrus and bilateral STG. In contrast, they enlarged in bilateral ACG. ***Conclusion:*** Chronic pain patients demonstrated abnormal rCBF distribution on both baseline and post SCS conditions. Increased rCBF of thalamus and precuneus under both conditions in the PR group and decreased rCBF of ACG under post SCS conditions in the GR group were characteristic patterns. Tc-99m-HMPAO SPECT with 3D-SSP and SEE analysis is likely objective and effective in monitoring and evaluating therapeutic outcome by SCS in chronic pain. In addition, it provides information that is useful in the selection of SCS candidates.

Key words: ^{99m}Tc-HMPAO SPECT, chronic pain, 3D-SSP, spinal cord stimulation (SCS), SEE analysis

INTRODUCTION

INTRACTABLE CHRONIC PAIN is categorized as a type of pain that continues for several months exceeding three to six months.[1] The origin is considered to be abnormal pain transmission or impairment of the pain control system per

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se.[1–3] It may be associated with reorganization and decreased activity of brain tissues at the pain controlling sites (disinhibition) resulting from plastic changes of peripheral and central nerves and increased excitation (sensitization/ hypersensitization) of nociceptive cells.[3,4]

As chronic pain worsens, psychological or mental disorders such as depression may appear.[3,5,6] Pain characterized by an increasingly chronic tendency contains fewer organic elements but more psychiatric factors.[7,8] Besides the general therapeutic interventions such as drug treatment and nerve block treatment, trans-dermal electrical nerve stimulation (TENS) and SCS are recommended as promising treatments for intractable pain.[9,10] SCS is a method to stimulate the spinal cord via the dura mater using an electrode implanted in the peridural space.[10] Although the analgesic mechanism has not been sufficiently clarified, the mechanism that controls the spinal cord works as a result of stimulation of the dorsal column and transmission of nociceptive stimulus in the dorsal horn of the spinal cord is inhibited or blocked.[11,12] Furthermore, association with descending pain control resulting from activation of the pretectal nucleus as the central regulation site of the analgesic system and inhibition of thalamus and upper central neurons have been suggested.[13] However, correct evaluation of therapeutic effect by SCS is difficult by conventional imaging modalities such as CT or MRI.

Recently, abnormal regional cerebral blood flow (rCBF) accompanying enhanced excitation of nociceptive cells and reduced neuronal activity at the pain control site has been pointed out as one of the pathological conditions of chronic pain.[14,15] The spino-thalamic tract and spino-reticular thalamic tract are the central stimulus conduction passages for the sense of pain.[16] This sense is projected to the post-central gyrus via the ventrobasal nucleus of the thalamus or to the basal ganglia or the cortical association area via the intra-laminal nuclei of the thalamus.[16] Examinations using positron emission tomography (PET),[15,17,18] functional magnetic resonance imaging (fMRI)[15,19,20] and SPECT have demonstrated abnormal rCBF in the pain cognitive areas such as thalamus,[14] island, cingulate gyrus, amygdaloid nucleus and the secondary somatosensory cortex (SII). Speculation exists that SCS therapy inhibits this conductive network resulting in an alteration of rCBF. To analyze the data more objectively, statistical image analyzing methods have been developed, such as 3D-SSP[21] and SPM.[22] While SPM analysis indicates foci with a significant difference over the whole brain, for activation analysis, 3D-SSP has a clinical purpose of diagnosing by detecting distribution forms abnormal Z score areas.[23] Previously, we tried to evaluate rCBF alteration in small numbers of chronic pain patients using SPM.[24] However, organic intracranial disorders such as thalamic hemorrhage were included in the subjects of the study group and important areas except significant rCBF changed area might have been overlooked.

Table 1 Clinical background of patients

	GR (n = 12)	PR (n = 6)
Age	45.3 ± 8.7	40.4 ± 11.8
Gender (M/F)	8/4	4/2
Diagnosis		
Spondylotic myelopathy	8	4
Stump pain	2	1
CRPS	1	0
OPLL	1	0
Sequela of operation	0	1
Morbidity period (mo)	13.6 ± 6.7	17.7 ± 9.7
VAS score (baseline)	6.7 ± 2.7	7.2 ± 3.5
Pain side (L/R)	5/4	2/3

GR: good responder, PR: poor responder, mo: months, L: left, R: right, VAS: visual analogue scale, CRPS: complex regional pain syndrome

In the current study, we reanalyzed the rCBF alteration in relation to chronic pain in a greater number of patients without intracranial organic lesions using 3D-SSP (Three-dimensional stereotactic surface projections) statistical image analysis.[21] In addition, we compared the differences between the rCBF distribution before and after SCS treatment and the efficacy of SPECT analysis in evaluating the outcome.

METHODS

Patients

A total of 18 patients including 13 males and 5 females with chronic pain were selected as the subjects of the present study. These patients were diagnosed with the following diseases: cervical spondylotic myelopathy (n = 12), stump pain (n = 3), pain as a sequela of operation for ossification of the posterior longitudinal ligament (OPLL) in the cervical region (n = 1), pain as a sequela of operation for right rotator cuff tears (n = 1) and Complex regional pain syndrome (n = 1). Their mean age was 47.5 ± 13.1 years old (33–63 years) and the mean morbidity period was six years and two months (Table 1).

For relieving the symptoms, we employed the therapeutic technique using epidural spinal cord stimulation (SCS) as before.[13] We implanted a stimulation electrode in the peridural space to induce dorsal column stimulation via the dura mater.[24] Stimulation parameters varied for each individual. Amplitude was set from 0.5 to 1.5 V, frequency was set from 5 to 25 pulses and pulse width was set from 150 to 250 μsec.[24] The patient himself was able to change the stimulation conditions in a range without discomfort. For the semi-quantitative analysis of the severity of pain and to evaluate the efficacy of SCS, the visual analogue scale (VAS) was used.[25] The patients whose VAS scores decreased by four points or more, or decreased to class four or lower were classified into the

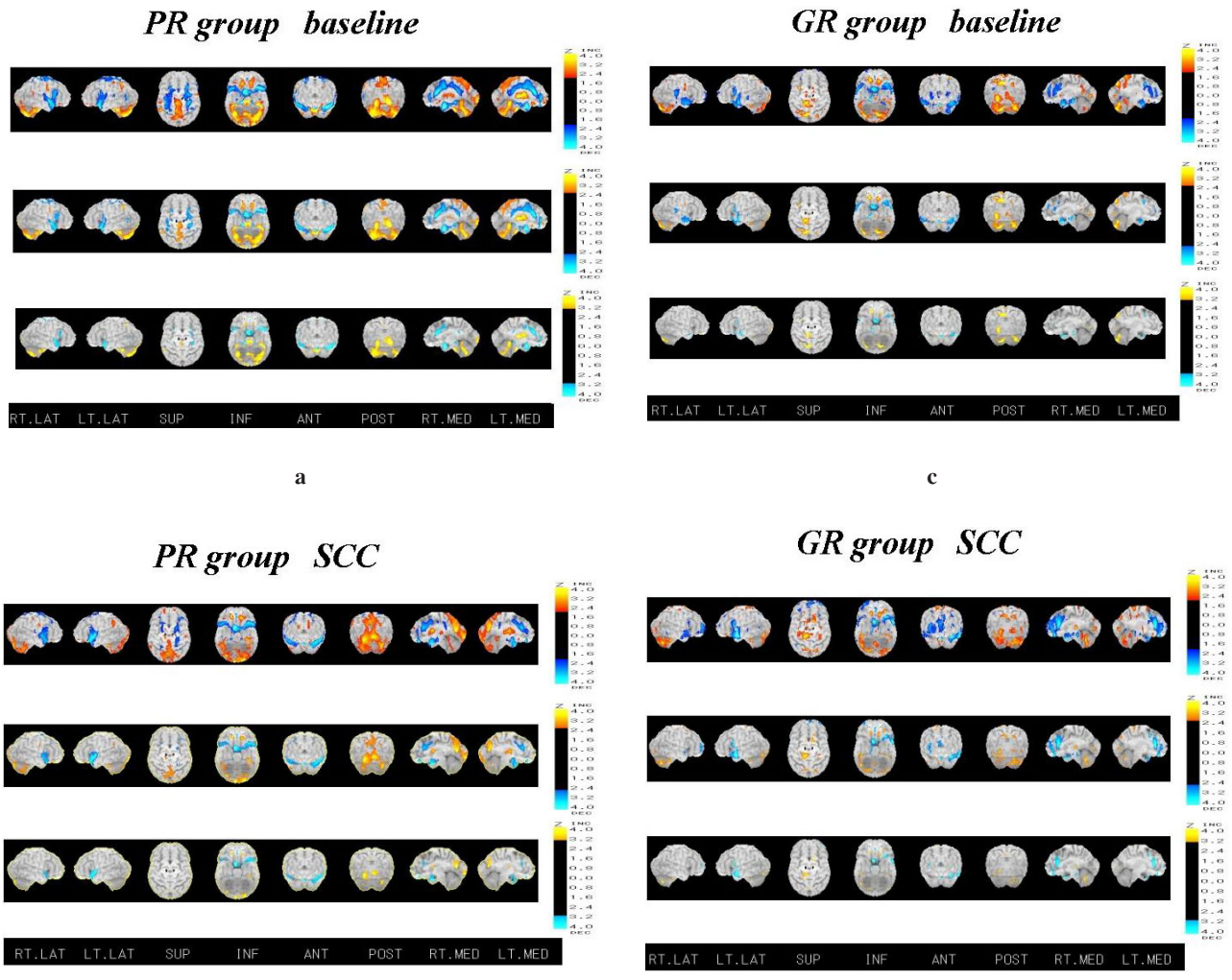

Fig. 1 Z score map. *Upper row;* lowest threshold > 2.0, *Middle row;* lowest threshold > 2.5, *Lower row;* lowest threshold > 3.0. a: Comparison of rCBF distribution between the PR group under the baseline condition and normal volunteers. Decreased rCBF was noted in bilateral ACG and superior temporal gyrus (STG). Under the condition with the lowest threshold > 3.0, both ACG and bilateral STG were still noted. Increased rCBF was noted in cerebellum, left thalamus and precuneus under each condition. b: Comparison of rCBF distribution between the PR group after SCS and normal volunteers. After SCS, increased rCBF area, left thalamus and cerebellum were localized but remained. The range of decreased rCBF of bilateral ACG and bilateral STG was also localized. c: Comparison of rCBF distribution between the GR group under the baseline condition and normal volunteers. It showed decreased rCBF in both ACG and STG, but the range was relatively smaller than in PR group. Increased rCBF was observed in bilateral cerebellum and precuneus. d: Comparison of rCBF distribution between the GR group after SCS and normal volunteers. The range of decreased rCBF in ACG was spread out in comparison with that in baseline condition.

good responder group (GR group). The patients whose VAS scores decreased by three points or less or remained at class five or more were classified into the poor responder group (PR group).[24] According to the treatment response, 12 patients were categorized into the GR group and the remaining 6 patients into the PR group (Table 1). There were no significant differences in the clinical characteristics between the two groups.

Image analysis

Before undergoing SPECT, all subjects received an intravenous line while lying down with their eyes closed. Each subject received a 600 MBq intravenous injection of ^{99m}Tc-HMPAO (HMPAO). Ten minutes after this injection, the brain perfusion SPECT was performed using a triple-head gamma camera (Prism 3000: Marconi) equipped with a high-resolution fan-beam collimator. For each camera, projection data were obtained in a 128 × 128

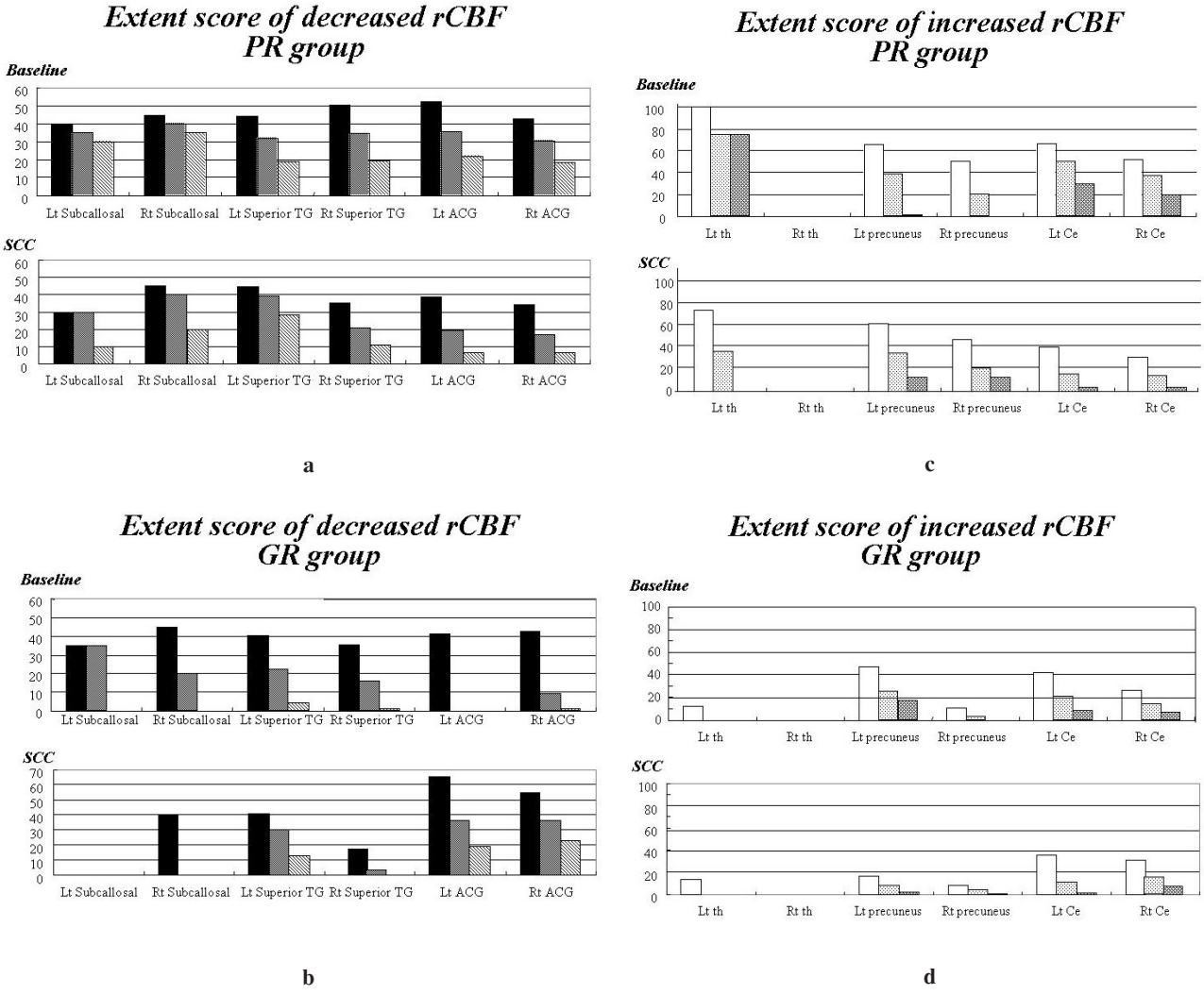

Fig. 2 a: Extent scores of decreased rCBF in PR group. In the baseline condition, the scores of bilateral subcallosal gyrus, bilateral STG and ACG were higher than 30% in condition with the threshold > 2.5. After SCS, these scores were relatively decreased but still remained in the same condition. b: Extent scores of decreased rCBF in GR group. Scores under the condition with the threshold more than 2.5 were around 20%. After SCS, the scores of ACG increased. In contrast, they decreased markedly in bilateral subcallosal gyrus and in the STG. c: Extent score of increased rCBF in PR group. Left thalamus showed more than 70% even in the condition with the threshold more than 3.0. Both bilateral precuneus and bilateral cerebellar hemispheres showed scores of around 40% under condition with the threshold more than 2.5. After SCS, each regional score decreased to around 20% respectively under the same condition. d: Extent score of increased rCBF in GR group. The score was 0% in this condition with the threshold more than 2.5 in thalamus, and both precuneus and cerebellum showed values around 20%. After SCS, the score of bilateral precuneus and left cerebellum decreased more. The right cerebellum did not show a prominent change.

format for 24 angles of 120° at 50 s per angle. A Shepp and Logan Hanning filter was used for SPECT image reconstruction at 0.7 cycles per centimeter. Attenuation correction was performed using Chang's method. SPECT analyses were conducted two days before treatment and five days after implantation of the electrodes in the epidural space near the area of the spinal cord. The post-therapeutic data were recorded under the stimulated conditions with SCS.

We used the adjusted rCBF images (normalization of global CBF for each subject to 50 ml/100 g/min with proportional scaling) to evaluate the alteration of relative rCBF distribution in chronic pain patients. The data were transferred to a personal computer with the interface software via the network for 3D-SSP analysis. Each group was compared to the normal data base, which was originally made in Miyazaki Medical College hospital, using unpaired t test. Normal data base was composed of 17

normal volunteers, 11 males and 6 females, mean age 43 ± 10.

Group comparison of rCBF distribution between the healthy volunteers and each subgroup (GR group or PR group) was done both under the baseline and under the post-SCS conditions. The threshold for abnormal rCBF was adjusted to 2.0, 2.5 and 3.0, that is, the areas whose Z score exceeded these thresholds were defined as an area showing abnormal rCBF distribution. For the quantitative analysis, we used segmental extraction estimation (SEE) to examine all the coordinates in the anatomically and functionally classified regions. We calculated a total of coordinate data with a Z-value exceeding the lower threshold of the three kinds of Z value (2.0, 2.5 and 3.0) set as a significant finding; the rate of the total coordinates with significantly decreased or increased Z-value in the total of coordinates in the respective segments (extent score).[23] In the Talairach Daemon, brain anatomy is classified into levels 1 to 5. Based on the low resolution of the SPECT system, we used the anatomical classification according to level 1, 2 and 3.[23] In the analysis with specific regions known to be related with pain, ACG and thalamus, we used the level 3, the gyrus level.[23] We compared extent score both under the baseline and in the post-SCS conditions in both the GR and the PR group.

RESULTS

Under the baseline conditions in the PR group, a decreased rCBF was noted in limbic lobe such as bilateral ACG and in subcallosal gyrus, and bilateral temporal lobe particularly in the superior temporal gyrus (STG) (Fig. 1a, Fig. 2a). Increased rCBF was noted in the left thalamus, part of the parietal lobe particularly in precuneus and cerebellum (Fig. 1a, Fig. 2c). After SCS, both decreased rCBF areas and increased areas were relatively localized. However, even in the condition with lower threshold >3.0, decreased rCBF areas remained variously. For the increased rCBF areas, they also remained with lower threshold >2.5. Interestingly, the extent score of bilateral precuneus increased in condition with lower threshold >3.0 (Fig. 1b).

In the GR group, decreased rCBF was also noted in bilateral STG, bilateral ACG and bilateral subcallosal gyrus under the baseline conditions with threshold >2.0. Under the lower threshold 2.5, both STG and subcallosal gyrus remained unchanged (Fig. 1b, Fig. 2b). Increased rCBF was noted in bilateral precuneus and bilateral cerebellum. These extent scores were lower than those of the PR group in the same condition mostly (Fig. 2d). Regarding decreased rCBF areas after SCS, the extent score of bilateral ACG increased. In contrast they prominently decreased in bilateral subcallosal gyrus (Fig. 1d, Fig. 2b). However, STG did not show marked change. As for the increased rCBF area, most regions disappeared or were markedly localized. The extent score decreased to less than 20% under condition with lower threshold 3.0 excluding right cerebellum (Fig. 2d).

DISCUSSION

The current study demonstrated abnormal rCBF distribution in a variety of regions even under the baseline condition. The results were similar to those of previous investigations.[15,18,19] Namely, alterations of rCBF in subcallosal gyrus, ACG, STG, thalamus, precuneus and cerebellum were considered to be characteristic findings.

The prominent difference of rCBF distribution between the GR group and the PR group was thalamic rCBF. Although increased rCBF was observed in the left thalamus in the PR group under the baseline condition, it was almost normal in the GR group. As thalamus is one of the major conduction areas for recognition and organizing the pain sensation system,[16,26] chronic pain stimulation via the thalamus seemed to cause rCBF increase as a result. The phenomenon probably reflects generalized arousal in reaction to pain.[15,18] Another explanation is that suppressive work from the cerebral cortical network to thalamus is disturbed and the activity of nociceptive receptor in the thalamus enhanced as a result of which rCBF increases.[27] Similar results were reported in previous PET studies.[27,28] After SCS, it was relatively localized but still remained in the PR group. In the GR group, it was still almost normal level. These result suggested that thalamic rCBF change is a convincing index of monitoring of SCS. It also may become an index of therapeutic adaptation.

The other increased rCBF area was noted in the posterior part of the bilateral parietal lobe particularly in precuneus. These areas unify the information of somatosensory sensation and regulate the next performance.[16] As such, these areas conduct the recognition of pain sensation. Increased rCBF of these areas reflects recognition and regulation of pain sensation. The extent score of PR group under the baseline is higher in comparison with that of the GR group. Furthermore, it remained unchanged in the PR group whereas extent score decreased in the GR group after SCS. These results support the contention that increased rCBF of precuneus is associated with pain recognition theoretically. The rCBF in precuneus can also become an index of SCS effect.

Similarly, increased rCBF was noted in cerebellum. According to a previous PET study, cerebellum is activated by deep brain stimulation in chronic pain.[18] The research supported our current result in part. The anterior lobe of the cerebellum receives input from the spinal cord and regulates the muscles.[16] The posterior lobe receives input from a wide range of the cerebral cortex via the pons and promotes smooth progress of voluntary movement.[16] The increased rCBF seemed to reflect modulated muscle tone regulation. In addition, there seems to exist in the neurological network with the pain perception area of the cerebral cortex and cerebellum.[18] Neuroanatomical

mapping of cerebellar projections has also revealed that they extend into the prefrontal cortex, which may provide the anatomical substrate for its cognitive and emotional functions.[29] Such various factors might contribute to the increase of cerebellar rCBF. As extent score decreased almost equally after SCS in both groups, it did not help in the differentiation of the therapeutic effect.

Both groups demonstrated decreased rCBF in bilateral ACG, which are known as sites playing an important role in the emotional profile of pain.[15,16,19,27,30,31] In addition, ACG is associated with loading of working memory that is an important mental function that supports a large variety of recognition processes from sensory and motion awareness to self consciousness.[32–34] There have been also various previous reports regarding the rCBF alteration in ACG in pain stimulation.[15,35,36] The neuronal activities of ACG seemed to be reduced as an inhibitive reaction for persistent unpleasant information such as chronic pain. The decreased rCBF of ACG in the baseline seemed to reflect the adaptation for an unpleasant pain of long duration. After SCS, an opposite tendency was noted between the two groups. In the GR group, the decreased rCBF area was extended. In the previous research, alteration of rCBF in ACG was reported after various stimulation therapies.[15,18] Ikemoto et al. reported that deactivation of ACG was shown after brain cortical activation in response to the improvement of chronic pain.[37] It may reflect the continuous suppressive regulation of the working memory to prevent persistence of the discomfort feeling. On the other hand, the region with decreased rCBF was reduced in size in the PR group. As the neuronal activity in ACG is the commonly activated in chronic pain patient,[37] rCBF increase in ACG might be associated with aggravation of discomfort owing to a contrary effect brought by SCS.

Subcallosal area is the localized limbic portion before ACC and also contributes to the emotional response.[38] Both groups showed decrease of rCBF in the subcallosal area, which was only observed by SEE analysis because of its narrowness. The extent score decreased in the GR group after SCS but it remained unchanged in the PR group. Although this phenomenon is different from that in ACG, this rCBF change also can become an index of the therapeutic effect of SCS.

A prominent decrease of rCBF was also demonstrated in the STG. This area contains one of the somatosensory areas. Morphologically, the somatosensory area consists of SmI (primary somatosensory area) that is adjacent to the central groove of the post-central gyrus and SmII (secondary somatosensory area) existing in the area, outside of SmI, ranging from the post-central gyrus to the operculum, and opercular part of parietal lobe.[16] SmI processes the information about the location of stimulus of pain, while SmII processes the information about the intensity of stimulus.[16] SmII plays important roles in the recognition of pain like SmI.[39] Decreased rCBF in SmII seemed to reflect the adaptation to control the pain recognition. Decreased rCBF areas were localized or diminished after SCS in the GR group. In contrast, the PR group did not show prominent change. As described above, decreased rCBF in those areas reflects pain modulation. This phenomenon seems to be due to the need of pain sensation relaxation in STG being decreased by SCS.

The limitation in the current study is the heterogeneity of patient's symptoms which is encompassed unilateral pain, bilateral pain or upper limb pain, and lower limb pain. Although rCBF change in the contra-lateral side is often reported when the symptoms are confined to the unilateral side, bilateral rCBF changes are also observed even in the patients with unilateral pain stimulation.[27,40,42] Ideally, further research with a large number of chronic pains with homogeneous symptoms should be undertaken in future studies. Further studies with more homogeneous patient populations, however, are necessary to predict the outcome of treatment and long-term prognosis.

One more limitation is the methodological problem using 3D-SSP. It seemed that thalamus played a large role in affiliation of pain. However, we observe only thalamic interior superficial blood flow in 3D-SSP, and evaluation of the whole internal structure may be insufficient. In the future, examination for a larger group will need software such as SPM which can evaluate the configuration of the thalamus inside.

The depressive state is another causative factor for rCBF alteration.[5–8] Generally, psycogenic factors such as anxiety, depression or memories of pain sensation are causative factors for pain.[8] It has been reported that approximately 30% of the patients suffer from complications such as hysteria, depression and hypochondria resulting from the stress due to chronic pain.[7] When these patients experience a depressive state associated with these symptoms, they notice new pain or aggravation of preexisting pain.[8] The alteration of rCBF is frequently seen in prefrontal cortices or ACG in depression.[43,44] Although no patient in the current study demonstrated prominent symptoms characteristic with depression, potentially present depressive state possibly promote the decrease in rCBF in these areas.

In summary, Tc-99m HMPAO SPECT with 3D-SSP and SEE analysis was an effective and objective method for monitoring the SCS effect of chronic pain. Based on the difference of rCBF distribution in ACC after SCS, rCBF alteration in ACC seemed to be an effective objectivity index of SCS effect. In addition, as the difference of rCBF distribution was noted particularly in thalamus and precuneus under the baseline condition, selection of candidates for SCS therapy may be facilitated by the interpretation of rCBF alteration in thalamus and precuneus.

CONCLUSION

We confirmed the abnormal distribution of rCBF in

patients with chronic pain in ACG, STG, subcallosal gyrus, thalamus, precuneus and cerebellum. After SCS, rCBF alteration showed a different pattern according to the therapeutic effect. Increased rCBF of thalamus and precuneus under both conditions in the PR group and decreased rCBF of ACG under post SCS conditions in the GR group were characteristic patterns.

Tc-99m-HMPAO SPECT with 3D-SSP and SEE analysis seemed to be an effective and objective method to monitor the therapeutic response by SCS in chronic pain. In addition, it might provide useful information for the selection of SCS candidates.

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