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Decreased perfusion of the bilateral thalami in patients with chronic pain detected by Tc-99m-ECD SPECT with statistical parametric mapping

Yoshiaki NAKABEPPU,* Masayuki NAKAJO,* Takashi GUSHIKEN,** Shinsaku TSUCHIMOCHI,* Atsushi TANI* and Yuuichi KANMURA**

*Departments of *Radiology and **Anesthesia, Faculty of Medicine, Kagoshima University*

The purpose of this study was to examine whether the Tc-99m-ECD SPECT can detect any difference between the brain perfusion in patients with chronic pain and normal controls by means of the Statistical Parametric Mapping (SPM96). The subjects were twelve patients with chronic pain (CP group) and twelve normal controls (NC group). After informed consent was obtained, 720 MBq of Tc-99m-ECD was intravenously injected as a bolus. The SPECT data were acquired once for 20 mins from 5 mins after i.v. injection of Tc-99m-ECD, with a triple-head rotating gamma camera. The SPECT data were transformed into a standard stereotactic space, and group comparisons between CP and NC groups were performed on a voxel-by-voxel basis. The subset of voxels exceeding a threshold of $p < 0.001$ in omnibus comparisons and remaining significant after correction for multiple comparison ($p < 0.05$) was displayed as a volume image rendered in three orthogonal projections. There was a significant decrease in perfusion in the bilateral thalami in the CP group, suggesting that perfusion in the thalamus generally decreases in patients with chronic pain. Tc-99m-ECD SPECT with SPM96 may be useful for studies of the mechanisms of chronic pain.

Key words: Tc-99m-ECD, chronic pain, brain perfusion, SPECT, SPM96

INTRODUCTION

DECREASED PERFUSION in the thalamus in patients with chronic pain was reported with positron emission tomography (PET).[1–3] There were some reports of studying patients with chronic pain by means of single photon emission computed tomography (SPECT) with Tc-99m-HMPAO.[4,5] Technetium-99m-L,L-ethyl cysteinate dimer (Tc-99m-ECD) is a relatively new agent for mapping brain perfusion by SPECT.[6,7] There was no report of brain perfusion in patients with chronic pain by Tc-99m-ECD. Recently a software package known as Statistical Parametric Mapping (SPM96) has been developed. It can not only spatially normalize PET or SPECT images to a standardized stereotactic space in an activation study, but can then also perform statistical analyses on groups.[8,9] This software allows reliable and objective image handling and data analysis, which definitely improves variability between studies due to the analytic process, itself. Here we use this technique to show the significant differences in brain perfusion between patients with chronic pain and normal controls by Tc-99m-ECD SPECT.

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For reprint contact: Yoshiaki Nakabeppu, M.D., Department of Radiology, Faculty of Medicine, Kagoshima University, 8–35–1 Sakuragaoka Kagoshima-shi, Kagoshima 890–8520, JAPAN.

MATERIALS AND METHODS

Subjects

The study population consisted of 12 normal controls (NC group) (male; 9, female; 3, and mean age; 37.4 ± 3.0 years) and 12 patients with chronic pain (CP group) (male; 7, female; 5, and mean age; 41.4 ± 18.8 years). The NC group consisted of medical staff who understood the research protocol and were willing to serve as normal controls. The data were collected from December 1998 to March 1999. None in the NC group had any neurological

Table 1 The location and etiology of patients with chronic pain

	Sex	Age	Location	Etiology
1	F	26	Lt. leg	Trauma
2	M	37	Bil. perineum	Trauma
3	M	39	Lt. chest wall	Herpes
4	F	15	Lt. hand	Trauma
5	M	55	Rt. face	Herpes
6	F	27	Lt. face	Herpes
7	M	61	Lt. leg	Trauma
8	F	38	Bil. leg	SLE
9	M	48	Rt. face	Herpes
10	F	16	Rt. knee	Trauma
11	M	37	Lt. face	Herpes
12	M	68	Lt. face	Herpes

Lt.: Left, Rt.: Right, Bil.: Bilateral, SLE: systemic lupus erythemadosus

abnormality or pain. None of the patients had any neurological abnormality other than chronic pain. The etiology and location of chronic pain in this study is shown in Table 1. Case 8, a patient with systemic lupus erythematosus (SLE) was off steroid drugs for over one year and had no history of encephalitis.

Dynamic data acquisition and SPECT study

After informed consent was obtained, each subject was kept supine with eyes closed under a single-head gamma camera (SNC-5100, Shimadzu) with a low energy parallel hole collimator. Seven hundred and twenty MBq of Tc-99m-ECD was intravenously injected as a bolus within a few seconds. Passage of the tracer from the aortic arch to the brain was monitored in a 64 × 64 matrix format for 120 seconds at one second intervals with the photo peak centered on 140 keV ± 20%. The data were used for calculation of mean of global cerebral blood flow (gCBF). Then the projection data for SPECT were acquired once for 20 minutes from 5 minutes after i.v. injection of Tc-99m-ECD, with a triple-head rotating gamma camera and fanbeam high-resolution collimators (PRISM-3000, Shimadzu) and the photo peak centered on 140 keV ± 10% in 90 projections with 360 degree rotation (128 × 128 matrix format). Each scan was performed in order to obtain transverse images, which were parallel to the line between the anterior and posterior commissures (AC-PC line).

Image reconstruction and analysis

At first gCBF was noninvasively measured by a graphic analysis without blood sampling[10,11] from the dynamic data obtained from each subject. The data were processed by means of a nuclear data processor (ODYSSEY, Shimadzu). The raw projection data were prefiltered with a Butterworth filter (cutoff frequency: 0.13 cycle/pixel, power factor: 8). The SPECT images were then reconstructed by a filtered back-projection algorithm. Attenuation correction was performed by assuming an elliptical outline of the head in each slice and uniform attenuation in the head ($\mu = 0.09$), and the outside of the elliptical outline of each slice was masked by 0 in order to reduce the effect of activity in the soft tissue. SPM96 for Unix was installed in the PC microcomputer [Pentium II (Intel) 350 MHz, Memory 256 M bytes, OS: Linux (kernel version: 2.0.30; Red Hat software, Inc., Research Triangle Park, NC)] in which MATLAB4.2c (Mathworks) had been installed. All images were transmitted to the PC microcomputer via a network. These images with ODYSSEY format were converted to images with byte swapped ANALYZE (MAYO Foundation) format, for use by SPM96. Then SPECT data were transformed into a standard stereotactic space by 12 parameter linear affine normalization and a further eight nonlinear iteration algorithm to a standardized stereotactic space (PET template, boundary: NMI) and the images were smoothed with an isotropic Gaussian filter (FWHM: 12 mm). The final image format was 16-bit/voxel with a size of 79 × 95 × 68 and voxel size of 2 × 2 × 2 mm. The stereotactically normalized regional CBF (rCBF) images were then adjusted for individual differences in gCBF (all images scaled to global mean rCBF: 50 ml/100 g/min for each subject with proportional scaling). Finally comparisons between NC and CP groups were performed on a voxel-by-voxel basis for all voxels common to all subjects. The set of values for these comparisons constituted a statistical parametric map of the t statistic SPM {t}. The SPM {t} maps were then transformed to the unit of normal distribution (SPM {Z}), and reached a threshold at $p = 0.001$. The subset of voxels exceeding a threshold of $p < 0.001$ in omnibus comparisons and remaining significant after corrective for multiple comparison (corrected $p < 0.05$) was displayed as a volume image rendered in three orthogonal projections.

RESULTS

In visual analysis, there was no definitive perfusion defect in SPECT images of all patients. The mean of gCBF was 41.4 ± 18.8 ml/100 g/min in the CP group and 47.4 ± 3.0 ml/100 g/min in the NC group as a result. There were no significant differences in mean gCBF and mean ages between CP and NC. In the comparison of rCBF processed with SPM96, there were significant decreases in perfusion in the bilateral thalami and possibly in part of the brain stem in the CP group when compared with the NC group (Figs. 1 and 2). There were no significant differences in any areas except the thalami and brain stem.

DISCUSSION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[12] There are three types

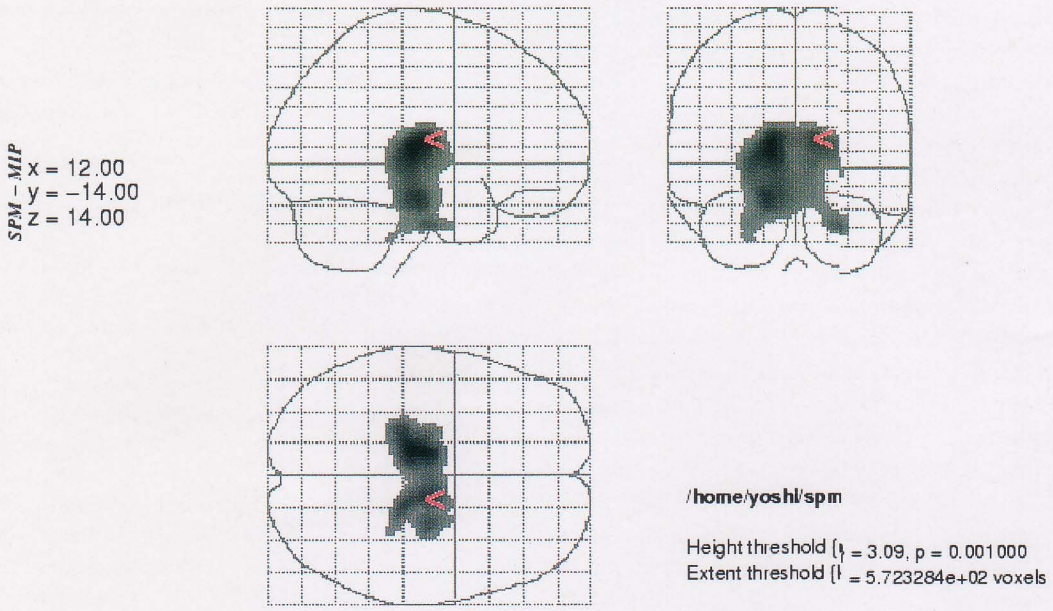

Fig. 1 Decreased rCBF (black area) is shown in the bilateral thalami of patients with chronic pain by statistical parametric mapping (SPM96) applied to Tc-99m-ECD SPECT.

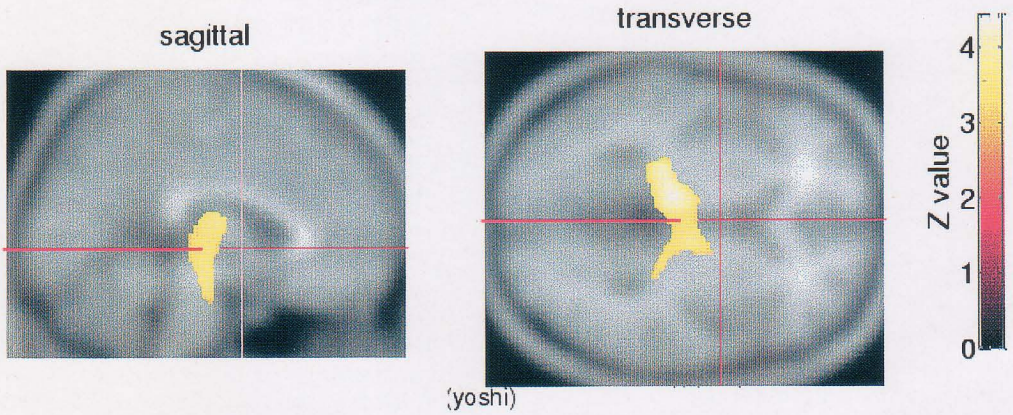

Fig. 2 Decreased rCBF is shown in the bilateral thalami and a part of the brain stem (yellow area) of patients with chronic pain on the MRI T1 images.

of pain[13]; transient pain is elicited by activation of nociceptive transducers in skin or other tissues of the body in the absence of any tissue damage, acute pain is elicited by substantial injury to body tissue and activation of nociceptive transducers at the site of local tissue damage, and chronic pain such as backpain, postherpetic neurialgia, and fibromyalgia, are commonly triggered by an injury or disease, but may be perpetuated by factors other than the cause of pain. Therefore it is difficult to estimate the difference in intensity between inter-patients with chronic pain. In addition, it is not the duration of pain that distinguishes the acute from chronic pain but, more importantly, the inability of the body to restore its physiological factors to normal homeostatic levels.[13] But, in this study, we defined chronic pain as pain which had continued for more than six months after relief of tissue damage or without tissue damage.

The thalamus is known to play an important role in the perception and integration of pain signals.[1–5,14–20] Decreased perfusion in the thalamus contralateral to the chronic pain side was reported with PET.[1–4] It was reported that acute pain induced increased thalamic perfusion.[15,18–20] Mountz et al. reported that the rCBF (region-to-cerebellum ratio) obtained with Tc-99m-HMPAO in the left and right thalami and left and right heads of the caudate nucleus was significantly lower in women with fibromyalgia which is characterized by widespread chronic musculoskeletal pain and fatigue.[4] Iadarola et al. reported that the reduction in rCBF was noted in the contralateral posterior thalamus and their observations suggest that a

type of learning such as an alternative process that makes the thalamo-cortical relay more efficient may occur, and chronic pain may be transmitted with less activity within the thalamus by this learning.[3] Di Piero et al. showed that decreased perfusion in the dorsal anterior quadrant of the thalamus contralateral to the site of pain was normalized after cordectomy by means of PET with $C^{15}O_2$.[1] Their results suggest that a decrease in blood flow in the contralateral thalamus means a reduction in total synaptic activity in the thalamus receiving the majority of the spinothalamic afferents from the painful side, and a return to a normal rCBF value after pain-relieving surgery (cordectomy) may be a functional effect of the increased spinothalamic input, and part of the normal tonic synaptic activity in the thalamus may be concerned with the inhibition of pain perception. Their data suggest that chronic pain may be related to pathophysiological mechanisms that abolish this normal inhibitory thalamic function. In our study, an area of significant decreased perfusion was expanded from the bilateral thalami to the upper portion of the brain stem. This suggests that a part of the brain stem connected with the thalami may also be influenced by chronic pain.

There were no significant differences in the mean of gCBF and the mean ages between the CP and NC groups as a result in our study: Therefore, the effects of differences between CP and NC groups in the mCBF and the mean age may be little, which might have affected the result of this study. In this study there were 7 patients with chronic pain on the left side, 3 on the right side and 2 on both sides. These numbers were too small to obtain any results about the effect of pain side. But asymmetric distribution of perfusion in the thalami in the present study may be due to the heterogeneity of the distribution in the location and the intensity of pain in the CP group. Further examinations are needed to complete statistical analyses to clarify the laterality of perfusion abnormality due to the pain side. Although it is possible that cerebral blood flow and neural activity are uncoupled during chronic pain, Tc-99m-ECD SPECT can detect the abnormality in perfusion in patients with chronic pain by means of SPM96. Although it is not possible to identify individual thalamic nuclei because of the low spatial resolution of SPECT, the Tc-99m-ECD SPECT study can be clinically performed more easily than PET.

CONCLUSION

Tc-99m-ECD SPECT can detect the difference between the NC and CP groups in brain perfusion by means of SPM96. The present study suggests that perfusion in the thalamus generally decreases in patients with chronic pain. Tc-99m-ECD brain perfusion SPECT with SPM96 may be useful for studies of the mechanisms of chronic pain.

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