Brain perfusion abnormality in patients with chronic pain

Tetsumi Honda,1 Toshihiko Maruta,2 and Kumiko Takahashi3

1 Department of Rehabilitation, Tokyo Metropolitan Rehabilitation Hospital, Tokyo, Japan (Present Affiliation: Department of Rehabilitation, Hamamatsu City Rehabilitation Hospital, Shizuoka, Japan)
2 Professor Emeritus, Department of Psychiatry, Mayo Clinic College of Medicine, Rochester, MN, U.S.A.
3 Department of Health Welfare, Takasaki Health Welfare University, Gunma, Japan

(Received for publication on January 23, 2007)  (Revised for publication on March 11, 2007)  (Accepted for publication on March 15, 2007)

Abstract. We performed single photon emission computed tomography (SPECT) of the brain in 15 patients with chronic pain (males, 7; females, 8; average age 49.1 ± 17.9 years) and identified the locus of cerebral blood flow reduction by a new analytical method (easy Z-score Imaging System: eZIS) to clarify the functional neuroanatomical basis of chronic pain. Of the 15 patients, 6 had backache, 2 neck pain, 2 gonalgia, and 5 pain at other sites, with an average Visual analog scale of pain (VAS) value of 6.1 ± 1.9.

In comparison with a data base on physically unimpaired persons, the dorsolateral prefrontal area (both sides, right dominant), medial prefrontal area (both sides), dorsal aspect of the anterior cingulate gyrus nociceptive cortex (both sides) and the lateral part of the orbitofrontal cortex (right side) were found to have blood flow reduction in the group of patients with chronic pain. As for chronic pain and its correlation with clinical features such as a depressive state, anticipation anxiety, PTSD, and conversion hysteria, the mechanism in the brain that was suggested by this study should be followed-up by functional neuroimaging studies. (Keio J Med 56 (2) : 48–52, June 2007)

Key words: chronic pain, frontal lobe, SPECT, eZIS, brain perfusion

Introduction

Chronic pain is one of the most challenging problems in contemporary medicine and has been studied in various settings and disciplines in clinical medicine, such as orthopaedics, psychiatry, and pain clinics.

In recent years, much new knowledge has accumulated on the mechanism in the brain of chronic pain through the development of non-invasive brain imaging procedures, including Single photon emission computed tomography (SPECT), PET, and fMRI.1 Through these procedures it has been clarified that the medial prefrontal area contributes to pain anticipation,2–4 and that the anterior cingulate gyrus contributes to the affective component of pain.5,6 Apkarian et al7 pointed out dysfunction of the orbitofrontal cortex in patients with chronic pain.

SPECT is simple and easy, but there have been problems related to differences in interpretation of results according to the experience of the radiologist, reproducibility, and difficulty in ascertaining three dimensionally the distribution of blood flow in the lesion. To overcome such weak points, statistical analysis of images has been introduced into SPECT diagnosis by transforming information on brain function of each person to eliminate individual differences in the configuration of the brain to recreate the normal brain of Talairach.

Representative procedures for statistical analysis of images obtained by SPECT are Statistical Parametric Mapping (SPM)8 and three-dimensional stereotactic surface projection (3D SSP) developed by Minoshima.9 However, as for the SPM, utilizing the t-test for analysis results in high specificity but low sensitivity. 3D SSP analyzes near partial blood flow to the brain surface and to reflect consequences to brain lists and presents difficulties in obtaining three dimensional positional information on aberrant blood flow.

To whom correspondence should be addressed: Tetsumi Honda, M.D., Ph.D., Hamamatsu City Rehabilitation Hospital, 1327-1 Wago-cho, Hamamatsu, Shizuoka 433-8511, Japan, E-mail: h-tetsu@mth.biglobe.ne.jp
In consideration of the above, Matsuda developed an easy Z-score imaging system (eZIS) that utilized the statistical procedure of 3D-SSP based on a version of SPM 99. E-ZIS can visualize differences in blood flow in the entire brain, including the deep brain, between a patient or patients under study and a control group derived from a database on 138 normal subjects (normal data base, NDB).

We performed SPECT on 15 chronic pain patients and analyzed the imaging data using eZIS. The purpose of this study is to clarify the intracerebral mechanism of chronic pain in patients with chronic pain using SPECT (eZIS) and to compare the results with those of previous studies.

### Subjects

Subjects were 15 consecutive chronic pain patients who received outpatient services at Tokyo Metropolitan Rehabilitation Hospital from May 2003 to June 2006. There were 7 males and 8 females ranging in age from 20-76 years (average, 49.1 ± 17.9). Duration of symptoms ranged from 6 months to 11 years (average 57.3 ± 38.7 months). Chief complaints were backache (sciatica) in 6, neck pain in 2, bilateral gonalgia in 2, and other regions in 5. Degree of awareness of pain using a visual analog scale (VAS) ranged from 2.1-9.8 (average, 6.1 (± 1.9)) (Table 1).

Subjects were diagnosed as chronic pain by a psychiatrist, and met the criteria for a “pain disorder” (chronic) of DSM IV -Tr. They had no past history of psychiatric illnesses and medication usage other than as-needed analgesics.

### Methods

Subjects were informed of the purpose of measuring blood flow with SPECT for further understanding of chronic pain and all agreed to participate in the study.

Brain SPECT with 99mTc-ethyl cysteinate dimmer (99mTc-ECD) was performed during bed rest with no stimulation and results were analyzed by eZIS. In eZIS, cerebral blood flow data on each subject were compared with age-matched NDB.

Degree of cerebral blood flow reduction is displayed as a Z score (Z score=(control mean)-(individual value)/(control SD) map. We averaged Z scores of all 15 chronic patients to obtain a common Z score map of chronic pain.

---

### Table 1. Subjects

<table>
<thead>
<tr>
<th>No</th>
<th>sex</th>
<th>age</th>
<th>Chief complaint</th>
<th>Medical diagnosis</th>
<th>Duration since onset</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>24</td>
<td>Low back pain</td>
<td>&quot;Chronic Low back pain&quot;</td>
<td>8 Y</td>
<td>6.9</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>26</td>
<td>Low back pain</td>
<td>Lumbar spine sequestration</td>
<td>11Y</td>
<td>6.4</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>66</td>
<td>Pudendal pain</td>
<td>Pudendal neuropathy</td>
<td>4Y6M</td>
<td>7.0</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>63</td>
<td>&quot;Ischias&quot;</td>
<td>Lumbar canal stenosis</td>
<td>6Y</td>
<td>7.0</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>76</td>
<td>Low back pain</td>
<td>Postoperative lumbar spine fracture fixation</td>
<td>4Y10M</td>
<td>4.4</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>52</td>
<td>Right leg pain</td>
<td>Morton disease</td>
<td>3Y7M</td>
<td>4.7</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>31</td>
<td>bil. Knee pain</td>
<td>bil. habitual patella dislocation</td>
<td>8Y</td>
<td>3.7</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>69</td>
<td>Bil. Arm pain</td>
<td>Bil. Shoulder periartitis</td>
<td>2Y</td>
<td>6.5</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>47</td>
<td>Low back pain</td>
<td>&quot;somatoform pain disorder&quot;</td>
<td>2Y4M</td>
<td>9.7</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>60</td>
<td>Neck pain</td>
<td>Cervical disc herniation</td>
<td>4Y11M</td>
<td>6.4</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>20</td>
<td>Left Arm pain</td>
<td>CRPS type 1</td>
<td>6M</td>
<td>5.4</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>34</td>
<td>Right shoulder pain</td>
<td>Cervical spine disk disorder</td>
<td>2Y</td>
<td>8.5</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>60</td>
<td>Low back pain</td>
<td>&quot;Chronic Low back pain&quot;</td>
<td>2Y</td>
<td>6.4</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>52</td>
<td>bil. Knee pain</td>
<td>&quot;bil.gonalgia&quot;</td>
<td>10Y</td>
<td>2.1</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>57</td>
<td>Neck pain</td>
<td>Cervical spine distorsion</td>
<td>1Y11M</td>
<td>6.2</td>
</tr>
</tbody>
</table>

VAS: Visual Analog Scale Value of Pain
Results (Fig. 1)

In the 15 chronic pain patients, decreased cerebral blood flow was observed in the dorsolateral prefrontal area (both sides, right dominant), medial (both sides), dorsal aspect of the anterior cingulate gyrus nociceptive cortex (both sides) and right lateral orbitofrontal cortex (right side).

Discussion

It is generally known that chronic pain is heterogeneous, and a correlation of symptomatology with depression or post-traumatic stress disorder (PTSD), panic disorder and conversion hysteria has been discussed. In fact, it is well-known that blood flow in the right dorsolateral prefrontal area decreases in the depressive state and the negative affective state during acute grief. The facts may suggest that CBF reduction in the dorsolateral prefrontal area (both sides, right dominant) commonly underlies in chronic pain, depression and acute grief.

The anterior cingulate gyrus consists of an ‘affect’ component and a ‘cognition’ component with regard to function, and the latter includes a skeletal muscle control cortex and a nociception cortex. Our results showed blood flow reduction in the nociception cortex of the anterior cingulate gyrus. On the other hand, in recent years dysfunction of the anterior cingulate gyrus has been noted in PTSD. This suggests that the mechanism of PTSD and chronic pain are related at the level of function of the dorsal aspect of the anterior cingulate gyrus as shown by the reduction of blood flow in this study.

The orbitofrontal cortex has an important function for the processing of rewards and punishments. Kringlebach and Rolls distinguished the orbitofrontal cortex into medial and lateral areas from neuroanatomical and functional considerations.
meta-analyses of neuroimaging studies as reported in the neuropsychology literature. They postulated that the lateral orbitofrontal cortex contributes to punishment irritation such as pain while the medial orbitofrontal cortex is related to monitoring of reward value (the same as above). In our study, blood flow reduction was found in the lateral orbitofrontal cortex in chronic pain patients. Recently, potency of “core dysfunction” in conversion hysteria was noted in the orbitofrontal cortex with cingulate gyrus. However, as is generally known, the clinical manifestations of conversion hysteria and chronic pain are complicated. Both findings of clinical observation and the relationship of the mechanism in brain of conversion hysteria and chronic pain must be reviewed carefully.

Although our results showed cerebral blood flow reduction of each part of the frontal lobe, the greatest manifestation of reduction was found in the right dorsolateral prefrontal area and the medial prefrontal area. How this finding contributes to the characteristics of chronic pain must be examined in the future.

Subjects of this study were those with chronic pain with a duration of more than six months, and were tested in a resting state without sensory stimulation. Increased blood flow in the prefrontal lobe was noted in acute and experimental pain. Therefore, the temporal profile of cerebral blood flow dynamics from the acute stage must be clarified in patients with pain.

Furthermore, it is necessary to study the relationship between improvement in clinical features and changes in images of brain function after therapeutic intervention.

Acknowledgements

We heartily thank the valuable support of Dr. Takeshi Takahata, vice director of Isehara Kyodo Hospital. In addition, we thank Mr. Hiroshi Tazumi in FUJIFILM RI Pharma Co., Ltd. and Mr. Kohei Toyota in Tokyo Metropolitan Rehabilitation Hospital for their technical assistance.

This study was funded by Grants for Activities Utilizing Investment Income from Accumulated Compulsory Automobile Liability Insurance Funds.

References

26. Devinsky O, Morrell MJ, Vogt BA: Contributions of anterior cin-
gulated cortex to behavior. Brain 1995; 118: 279–306