ORIGINAL ARTICLE

Brain perfusion abnormality in patients with chronic pain

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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 information on 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 al* [7] 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.

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Table 1. Subjects

No	sex	age	Chief complaint	Medical diagnosis	Duration since onset	VAS
1	M	24	Low back pain	"Chronic Low back pain"	8 Y	6.9
2	F	26	Low back pain	Lumbar spine sequestration	11Y	6.4
3	M	66	Pudendal pain	Pudendal neuropthy	4Y6M	7.0
4	F	63	"Ischias"	Lumber canal stenosis	6Y	7.0
5	M	76	Low back pain	Postoperative lumbar spine fracture fixation	4Y10M	4.4
6	F	52	Right leg pain	Morton disease	3Y7M	4.7
7	M	31	bil. Knee pain	bil. habitual patella dislocation	8Y	3.7
8	F	69	Bil. Arm pain	Bil.Shoulder periarthritis	2Y	6.5
9	M	47	Low back pain	"somatoform pain disorder"	2Y4M	9.7
10	M	60	Neck pain	Cervical disc herniation	4Y11M	6.4
11	M	20	Left Arm pain	CRPS type1	6M	5.4
12	F	34	Right shoulder pain	Cervical spine disk disorder	2Y	8.5
13	F	60	Low back pain	"Chronic Low back pain"	2Y	6.4
14	F	52	bil. Knee pain	"bil.gonalgia"	10Y	2.1
15	F	57	Neck pain	Cervical spine distorsion	1Y11M	6.2

VAS: Visual Analog Scale Value of Pain

In consideration of the above, Matsuda developed an easy Z-score imaging system (eZIS) [10] 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 data base 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[11]. 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.

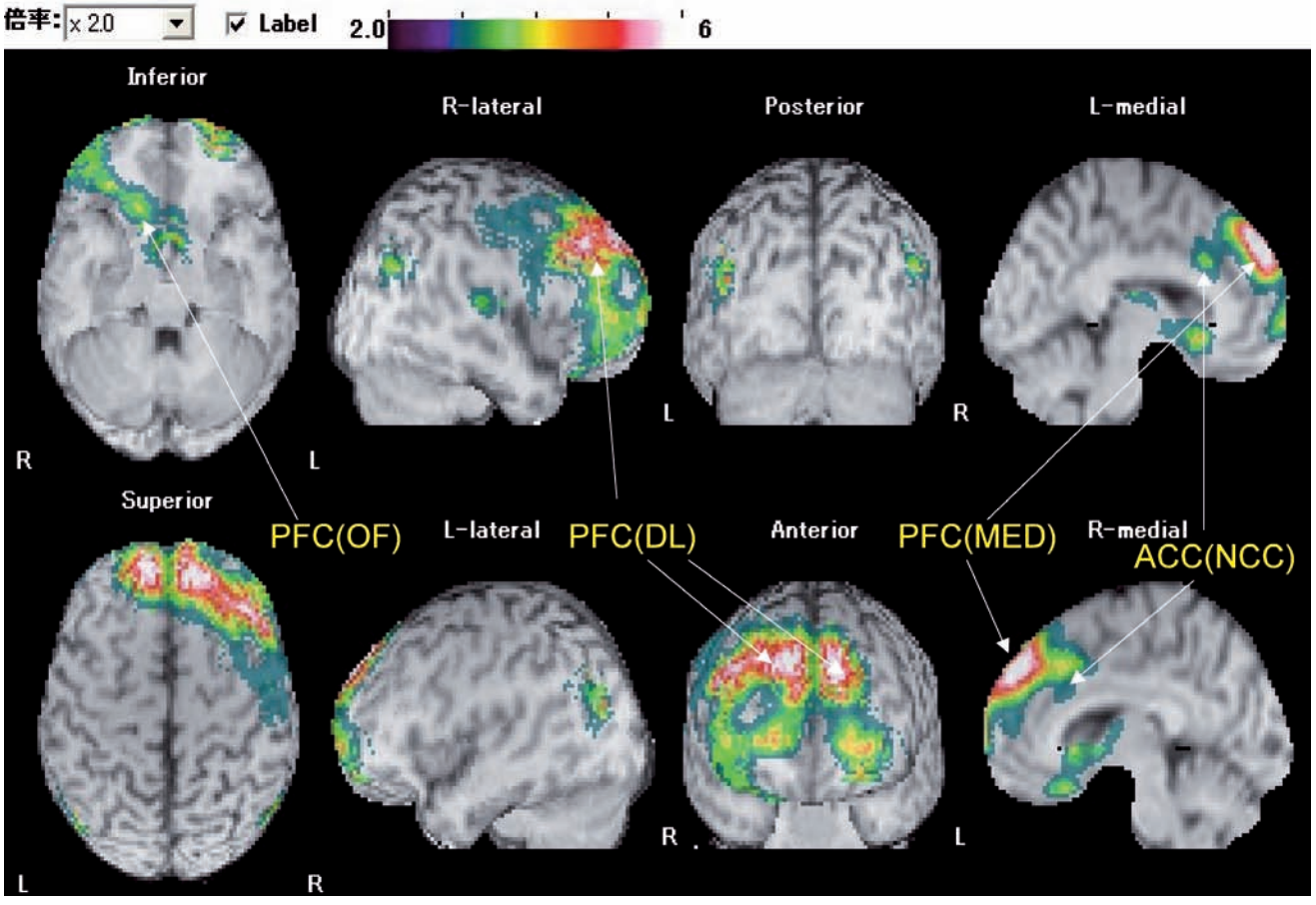

Fig. 1 Decreased blood flow was observed in the dorsolateral prefrontal area (both sides, right dominant), medial(both sides), dorsal aspect of the anterior cingulate gyrus nociceptive cortex (both sides) and right lateral orbitofrontal cortex (text).
PFC(MED) : medial prefrontal cortex
PFC(DL) : dorsolateral prefrontal cortex
PFC(OF) : orbitofrontal cortex
ACC(NCC) : anterior cingulate cortex (nociceptive cortex)

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 and lateral orbitofrontal cortex (right side).

Discussion

It is generally known that chronic pain is heterogenous,[12] and a correlation of symptomatology with depression[13–16] or post-traumatic stress disorder (PTSD),[17,18] panic disorder[19,20] and conversion hysteria[21–24] 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.[25] 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.[26] 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.[27,28] 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.[29] Kringekbach and Roll[29] distinguished the orbitofrontal cortex into medial and lateral areas from neuroanatomical and

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.[30] 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.[31,32] 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.

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References

1. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK: Human brain mechanisms of pain percptaion and regulation in health and disease. European Journal of Pain 2005; 9: 463–484
2. Ploghaus A, Tracey I, Gati JS,Clare S,Menon RS, Matthews PM, Rawlins JN: Dissociating pain from its anticipation in the human brain. Science 1999; 284: 1979–1981
3. Simpson JR Jr., Drevcets WC, Snyder AZ, Gusnard DA, Raichle ME: Emotion-induced changes in human prefrontal cortex Ⅱ. During anticipatory anxiety. Proc Natl Acad Sci USA 2001; 98: 688–693
4. Porro CA, Baraldi P, Pagnonni G, Serafini M, Facchin P, Maieron M, Nichelli P: Does anticipation of pain affect cortical nociceptive systems ? J Nerosci 2002; 22: 3206–3214
5. Rinville P, Duncan GH, Pricw DD, Carrier B, Bushnell MC: Pain affect encorded in human anterior cingulate but not somatosensory cortex. Science 1997; 277: 968–971
6. Price DD: Psychological and neural mechanisms of the affective dimention of pain. Science 2000; 288:1769–1771
7. Apkarian AV, Sosa Y, Krauss BR, Thomas PS, Fredrickson BE, Levy RE, Harden RN, Chialvo DR: Chronic pain patients are impaired on an emotional decision-making task. Pain 2004; 108: 129–136
8. Friston KJ: Analyzing brain images; principles and overview, in Human brain function, 1st ed. by Frackowiak RS, Friston KJ, Frith CD, Dolan R, and Mazziotta JC. Academic Press, San Diego 1997, 25–41
9. Minoshima S, Koeppe RA ,Frey A, Kuhl DE: Anatomical standardization; Liniar scaling and nonlinear warping pgi functional brain images. J. Nucl. Med 1993; 35: 1528–1537
10. Matsuda H, Mizumura S, Soma T, Takemura N: Conversion of brain SPECT images between different collimators and reconstruction process for analysis using statistical parametric mapping. Nuclear Medicine Communications 2004; 25: 67–74
11. American Psychiatric Association, Quick Reference to the Diagnostic Criteria from DSM-Ⅳ-TR 2000(Japanese edition by Igaku-Shoin Ltd. Tokyo 2002)
12. Turk DC: The potential of treatment mathing for subgroups of patients with chronic pain. Clin Pain 2005; 21: 44–55
13. Maruta T, Swanson DW, Swenson WM: Pain as a psychiatric symptom: comparison between low back pain and depression. Psychosom 1976; 17: 123–127
14. Leo RJ: Chronic pain and comobid depression. Curr Treat Options Neurol 2005; 7: 403–412
15. Arnow BA, Hunkeler EM Blasey CM:Comorbid depression, chronic pain, and disability in primary care, Psychosom Med, 2006; 68: 262–268
16. Neuhauser H, Ellert U, Ziese T: Chronic back pain in the general population in Germany 2002/2003: prevalence and highly affected population groups. Gesundheitswesen 2005; 67: 685–693
17. Sansone RA, Pole M, Dakroub H, Butler M: Childhood trauma, borderline personality symptomatology, and psychophysiological and pain disorders in adulthood. Psychosomatics 2006; 47: 158–162
18. Arguelles LM, Buchwald DS, Buchwald DS, Clauw DJ, Furner S Goldberg J: A twin study of postrraumatic stress disorder symptoms and chronic widespread pain 2006 (Epub ahead of print)
19. Hajistavoropoulos HD, LaChapelle DL: Extent and nature of anxiety experienced during physical examination of chronic low back pain. Behav res Ther 2000; 38: 13–29
20. McWilliams LA, Cox BJ, Enns MW: Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. Pain 2003; 106:127–133
21. Kapfhammer HP, Dobmeier P, Mayer C, Rothenhausler HB: Conversion syndromes in neurology. A psychopathological and psychodynamic differentitation of conversion disorder, somatization disorder and factitious disorder. Psyxhother Psychosom Med Psychol 1998; 48: 463–474
22. Cardenas DD, Larson J, Egan KJ: Hysterical paralysis in the upper extremity of chronic pain patients. Arch Phys Med Rehabil 1986; 67: 190–193
23. Doering S, Sollner W: Psychosomatic aspects of chronic pain. Orthopade 1997; 26: 521–527
24. Van Houdenhove B: Hysteria,depression and the nosological problems of chronic pain. Acta Psychiatr Belg 1988; 88: 419–430
25. Liotti M, Mayberg HS: The role of functional neuroimaging in the neuropsychology of depression. J Clinical and Experimental Neuropsychology 2001; 23: 121–136
26. Devinsky O, Morrell MJ, Vogt BA: Contributions of anterior cin-

gulated cortex to behavior. Brain 1995; 118: 279–306
27. Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS: Neural Correlates of Memories of Childhood Sexual Abuse in Women With and Without Posttraumatic Stress Disorder. Am J Psychiatry 1999; 156: 1787–1795
28. Lanius RA, Willamson PC, Densmore M, Boksman K, Gupta MA, Gati JS, Menon RS: Neural Correlates of Traumatic Memories in Posttraumatic Stress Disorder: A Functional MRI Investigation. Am J Psychiatry 2001; 158: 1920-1922
29. Kringekbach ML, Roll ET: The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Nerobiol 2004; 72: 341–372
30. Vuilleumer P: Hysterical conversion and brain function. Prog Brain Res 2005; 150: 309–329
31. Derbyshire SW, Jones AK, Collins M, Frinmann C, Harris M: Cerebral responses to pain in patients suffering acute post-dental extraction pain measured by positron emission tomography(PET). Eur J Pain 1999; 3: 103–113
32. Jones AK, Brown WD, Friston KJ, Qi LY, Frackowak RS: Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc Biol Sci 1991; 244: 39–44