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Ⅳ. 研究成果の刊行物・別刷

Alterations of Contralateral Thalamic Perfusion in Neuropathic Pain

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Abstract: Contralateral thalamus, the place of termination of spinothalamic tract, is affected in patients with pain. We employed single photon emission computed tomography (SPECT) to evaluate the thalamic perfusion in patients with spontaneous neuropathic pain. Ten patients with complex regional pain syndrome (CRPS) and eleven radiculopathiy patients were enrolled in this study. Regional cerebral blood flow of thalamus was assessed bilaterally by iodine-123-labelled iodoamphetamine SPECT. To standardize the inter-patient data, we set a contralateral thalamic uptake index (CTUI) for assessing thalamic asymmetry. In one study, we found elevation of CTUI in patients with symptoms of neuropathic pain for less than 12 month, whereas no change was observed in the case of a longer lasting disease. An another study demonstrated decrease of CTUI after pain treatment, even though it was unrelated to the pain intensity prior to treatment. Our SPECT study revealed that neuropathic pain altered thalamic neuronal activity. CTUIs were increased in early stage of the disease but decreased as the disease progressed to the chronic stage. These results suggest that CTUI can be used to improve management of neuropathic pain for proper evaluation of spontaneous pain.

Keywords: Brain imaging, regional cerebral blood flow, reflex sympathetic dystrophy, pain.

INTRODUCTION

Although neuromuscular disorders are manifested by a variety of clinical symptoms, pain is among those that are particularly hard to endure. Symptoms of pain are believed to have both central and peripheral origin and were studied with the help of neurophysiological and histocytochemical techniques [1, 2]. A number of animal models of spine-related diseases, such as radiculopathy, spinal stenosis, etc., was also introduced to explore the pathways of pain and to examine other related changes [3-5]. These studies were primarily focused on spinal cord due to its accessibility. Limited attention has been paid so far to the brain as well as few studies were undertaken in clinical settings.

In the past decade, several brain imaging techniques, namely single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional MRI (fMRI), emerged as powerful tools used to explore the biology of brain and to diagnose its pathological conditions [6-8]. Since fMRI technology is based on measuring hemodynamic response related to neural activity in the brain, it has advantages in detecting neuroanatomies responded to consecutive functional tasks such as pain stimuli. On the other hand, temporal resolution of SPECT and PET are similarly lower than fMRI technology and beneficial usage of these technologies are rather static brain activation corresponding to spontaneous pain. Although PET enables better resolution, SPECT, is a more affordable and widely used tool. These techniques are informative, noninvasive and extrapolate brain function from changes in the regional cerebral blood flow (rCBF), since it is spatially and temporally coupled to brain activity. Then, three dimensional data are mapped onto the cerebral anatomy.

It was shown that several brain structures, such as bilateral thalamus, insular cortex, cingulate cortex, primary (SI) and secondary (SII) sensory cortex, are activated by noxious cutaneous stimuli in normal subjects [9-13]. Among them, thalamus is viewed as a particularly important one, because spinothalamic tract, a major pathway of pain, terminates into the medial and lateral thalamic nuclei [14]. Clinical studies, however, reported opposite findings. Iadarola *et al.* found significant decrease in thalamic activity contralateral to symptomatic side in PET scans of patients with neuropathic pain [15]. Similar results were obtained for the patients with chronic cancer pain [16]. Therefore, one might assume that changes of contralateral thalamic activity and chronic neuropathic pain are presumably linked. In the present study, we used SPECT to examine whether a relationship exists between contralateral thalamic activity and neuropathic pain in patients with CRPS and radiculopathy.

MATERIALS AND METHODOLOGYS

Subjects

Twenty-one patients with neuropathic pain including ten with complex regional pain syndrome (CRPS) (seven men and three women; aged 27-65 years; time since the onset of

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symptoms 6-34 month) and eleven with either cervical or lumbar radiculopathy (six men and five women; aged 35-74 years; time since the onset of symptoms 0.3-30 month) who agreed with the study protocol were examined. Twenty two healthy volunteers with matching sex and age served as control. All patients had spontaneous pain and sensory impairments only in unilateral upper or lower extremities. Pain status of each patient was evaluated by the visual analogue scale (VAS). rCBF of the contralateral thalamus was assessed by means of Iodine-123-labelled iodoamphetamine single photon emission computed tomography (SPECT). The absence of previous cerebral vascular and psychological diseases was confirmed using brain computed tomography or magnetic resonance imaging by a psychiatrist not involved into the present study.

All protocols were conducted in accordance with the recommendations outlined in the Declarations of Helsinki and were approved by the local Medical Ethical Committee. All subjects signed an informed consent form prior to the examination.

Procedure

SPECT scanning started 10 min after intravenous injection of Iodine-123-labelled iodoamphetamine (111MBq) using an ultra high resolution fanbeam collimators equipped with a triple-detector SPECT device (Toshiba GCA9300A/HG, Tokyo, Japan). Size of field of view used in this study was 409.6mm x 409.6mm. Acquired SPECT images (128 x 128 matrices; 6 mm slice) were transferred to a Windows PC and then reconstructed from projection data by a filtered backprojection technique with Butterworth and Ramp filters according to Talairach brain atlas.

Measurement of CTUI and Image Analysis

Activity of contralateral thalamus was evaluated by calculating the contralateral thalamic uptake index (CTUI). Its measurement consisted of the following steps: a) after setting the identical region of interest (ROI) over the both thalami, rCBF corresponding to it was measured bilaterally; b) thalamic perfusion was standardized by subtracting rCBF of the whole brain to rCBF in ipsilateral and contralateral thalami, respectively; c) CTUI was calculated as the ratio of contralateral to ipsilateral thalamic uptake (Fig. **1A**). ROI was then separated into the medial and lateral subdivisions using the three dimensional stereotaxic ROI template (3DSRT) (Fig. **1B**). Indexes of both subdivisions (CTMUI and CTLUI respectively) were analyzed employing "NIH image" software (developed at the Research Service Branch (RSB) of the National Institute of Mental Health (NIMH), part of the National Institutes of Health (NIH)). Besides, relations between contralateral thalamic uptake index versus disease duration and pain intensity were examined. In controls, the indexes were calculated as the ratio of left to right consecutive thalamic uptakes.

Statistical Analysis

Results were analyzed using Wilcoxon matched pairs and Mann-Whitney tests.

RESULTS

In controls, all CTUI measurements showed symmetric thalamic perfusion (1.17±0.63).

CTUI and Duration of Disease

The most significant increase of CTUI was observed in patients with duration of symptoms of pain for less than 12 months. The average of CTUI was 1.94±1.01, P=0.0166 and in some cases even as high as >3. In contrast, the average of CTUIs in patients with a longer lasting disease (more than 12 month) was similar to controls (1.06 ± 0.45) (Fig. **2**).

Subdivision analysis was resulted no significant change in both CMTUI and CLTUI in patients with duration of disease for more than 12 month compare to controls. Although not statistically significant (P=0.067), an increase

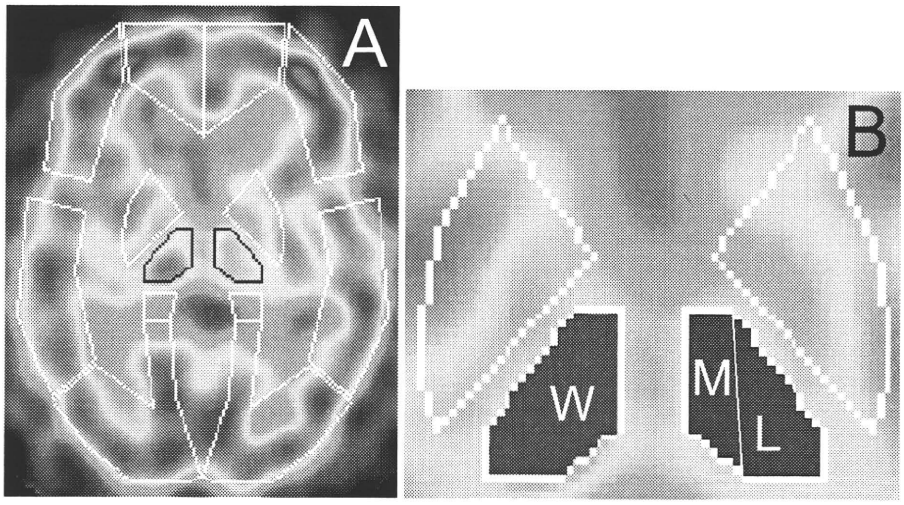

Fig. (1). Standardized brain SPECT images showing presets of ROIs template of 3DSRT (**A**) and subdivisions of thalamus used for CTUI measurements (**B**). ROI over thalami is outlined in black. Whole thalamus is marked as (W), medial and lateral parts as (M) and (L) respectively.

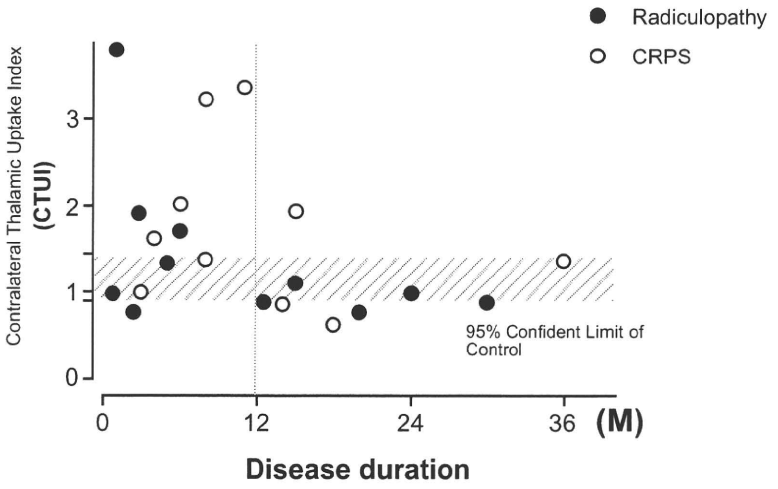

Fig. (2). Scatter gram showing relation between CTUI and disease duration. A significant increase of CTUI is seen for patients with the duration of disease for less than 12 month.

of CMTUI, but not of CLTUI, was observed in patients with duration of disease for less than 12 month (Fig. **3**).

CTUI and Intensity of Pain

In patients with either CRPS or radiculopathy, CTUI and pain intensity, measured by VAS, did not show a clear correlation between each other (VAS=3.5-7.8, average 5,4) (VAS=3.0-7.5, average 4.7), respectively (Fig. **4**).

DISCUSSION

We employed SPECT technique to determine regional concentration of radionuclide in thalamus as a function of time and then to compare its values in normal subjects versus in patients with neuropathic pain. It was observed that contralateral thalamic uptake index (CTUI) is elevated in patients with symptoms of neuropathic pain for less than 12 month. It was also detected that CTUI decreases as a result of pain treatment and that its values in patients with symptoms of pain for more than 12 month are in the range of those in control subjects. This attenuation of the contralateral thalamic activity in chronic pain status has been reported in other investigators. This inhibited thalamic activity might be related to pain pathogenesis, a reversal of this change would be expected as a correlate of pain relief. Accordingly, thalamic hypoactivity has been shown to be reversed by a number of analgesic interventions, from lidocaine blocks to neurosurgical procedures [17-22].

Activation of thalamus in response to acute noxious stimulation as a phenomenon of functional reorganization of central sensory neurons was described previously in both human and animal studies [23-27]. The consensus, however, whether the activation occurs uni- or bi-laterally was not reached. It was also not determined what side of the brain, if uni-laterally, is activated. Our results show that the methodology used to determine thalamic activation by measuring the regional blood flow is of critical importance here. We observed that raw data of thalamic blood flow

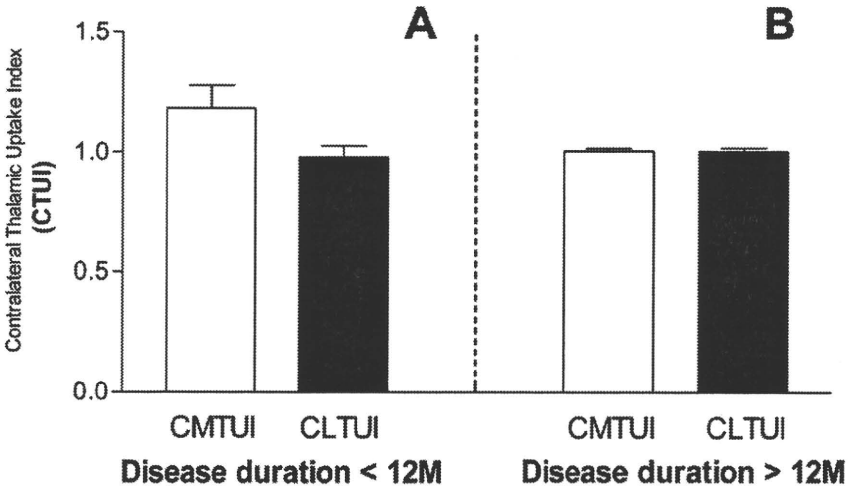

Fig. (3). Changes of CTUI in medial (CMTUI) and lateral (CLTUI) portions of contralateral thalamus in relation to disease duration. An increase of CTUI in medial contralateral thalamus is observed in the case of disease duration for less than 12 month (**A**). No changes between medial and lateral portions are detected in the case of disease duration for longer than 12 month (**B**).

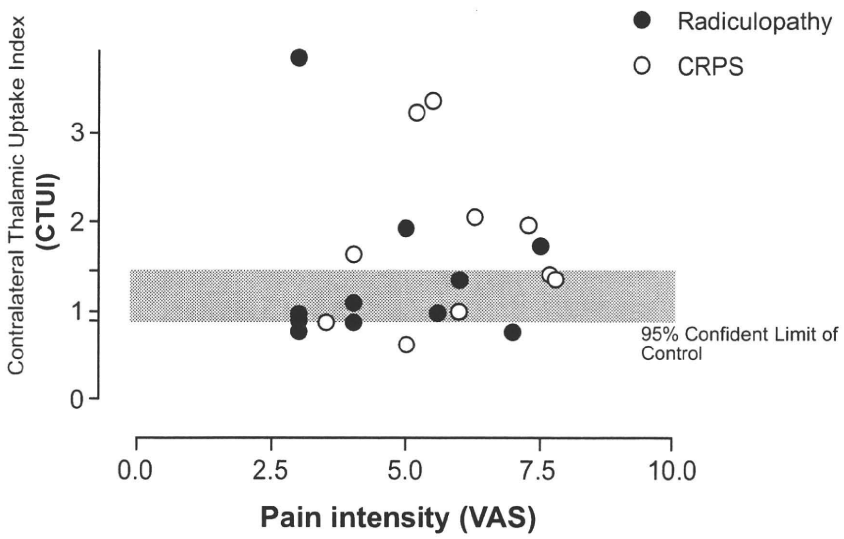

Fig. (4). Scatter gram demonstrating relation between CTUI and pain intensity (VAS). No correlation between pain CTUI and VAS can be found.

obtained from different subjects are not comparable due to significant individual variations. Therefore, we took a different approach and evaluated CTUI by comparing ratios of the total cerebral blood flow against the thalamic blood flow. Using this technique, it was possible to obtain data indicative of an involvement of contralateral thalamus in neuropathic pain. This conclusion is supported by the results of electrophysiological and morphological experiments in primates showing that sensory signals, including noxious inputs, terminate mainly in contralateral thalamus, with less than 10 percent of sensory afferents projecting ipsilaterally [28]. Furthermore, we found an increase of CTUI in the medial portion of contralateral thalamus (CMTUI), but not in the lateral portion, (CLTUI). In this respect, it should be mentioned that medial thalamus is viewed as a portion of thalamus linked to the "affective/motivational" aspect of pain, while lateral is related to "discriminative" pain. Therefore, it is likely that the former aspect of pain sensation is involved the most in patients with neuropathic pain. Additional studies that employ the fine spatial resolution brain imaging tools should help in clarifying this issue further.

Interestingly, we observed that activation of contralateral thalamus depends on the duration of disease and tends to decrease after 12 month since patients report their first complaints. How this observation can be explained? It is possible that sensory cortex adapts to the input of pain in such a way that hyper activation of thalamus for nociceptive transmission and cognition is no longer necessary [29] and /or that continuous pain affects intra-cranial blood distribution and thus results in the sensory blood uncoupling near the activated region [15]. It should be mentioned, however, that the pattern of thalamic reaction in this group of patients is likely to be a very complex issue that requires additional studies considering the possible involvement of other regions of the brain. In recent study, Honda *et al.* [30] focused on to prefrontal area and cingulate area, and found reduction of cerebral blood flow in chronic pain patients as well.

CONCLUSION

We utilized contralateral thalamic uptake index (CTUI) to detect changes of thalamic activity in neuropathic pain. CTUIs were increased in the early stage of the disease but decreased as the disease progressed to the chronic stage. Present results suggest that the activity of contralateral thalamus may have a role in development/maintenance of the chronic pain conditions.

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ORIGINAL ARTICLE

Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine

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Abstract

Purpose Painful neuropathic conditions of cancer pain often show little response to nonopioid and opioid analgesics but may be eased by antidepressants and anticonvulsants. Although gabapentin is effective in the treatment of neuropathic pain in patients with cancer, some patients experience intolerable side effects sufficient to warrant discontinuation. The aim of this study was to see whether low-dose gabapentin is effective in treating cancer-related neuropathic pain when combined with low-dose imipramine.

Methods Fifty-two cancer patients diagnosed as having neuropathic pain were allocated into four groups: G400-I group took gabapentin 200 mg and imipramine 10 mg every 12 h orally; G400 group took gabapentin 200 mg every 12 h orally; G800 group took gabapentin 400 mg every 12 h orally; I group took imipramine 10 mg every 12 h orally.

Results Low-dose gabapentin–imipramine significantly decreased the total pain score and daily paroxysmal pain episodes. Several patients developed mild adverse symptoms in the four groups, and three patients discontinued treatment due to severe adverse events in the G800 group.

Conclusion Low-dose gabapentin–antidepressant combination with opioids was effective in managing neuropathic cancer pain without severe adverse effects.

Keywords Cancer pain · Neuropathic pain · Antidepressant and anticonvulsants · Gabapentin

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Introduction

Neuropathic pain, producing a burning, shooting, or aching sensation with or without paresthesia, results from dysfunction of peripheral and central nerves [1, 2]. Opioid analgesics show good response in the treatment of neuropathic pain of nonmalignant origin [3]. However, painful neuropathic conditions of cancer pain often show little response to nonopioid and opioid analgesics but may be eased by adjuvants such as antidepressant and anticonvulsants [4–6].

Gabapentin is an anticonvulsant that binds to the a2-d subunit of voltage-gated calcium channels, decreasing the release of glutamate, norepinephrine, and substance P [1, 6]. Although it is effective in treating not only noncancer- but also cancer-related neuropathic pain [7, 8], some patients experience intolerable side effects sufficient to warrant discontinuation [1]. The incidence of side effects warranting its discontinuation is about 10–45% [1, 9]. We experienced some patients reporting somnolence and dizziness even when doses <800 mg are used, thereby discontinuing gabapentin in our daily clinical practice. However, a review article suggests that combination pharmacotherapy provide greater benefits [10]. In fact, when doses <600 mg are combined with antidepressants, gabapentin is effective in treating cancer-related neuropathic pain without severe side effects in our experience.

Table 1 Demographics and baseline characteristics of patients

	G400-I (n = 14)	G400 (n = 14)	G800 (n = 12)	I (n = 12)	p value
Age (year)	65 (58–73)	67.5 (64–70)	69 (65.5–71.5)	65 (60.5–79)	0.872
Sex (M/F)	9/5	10/4	9/3	6/6	0.573
Weight (kg)	51.5 (46–61)	52 (50–60)	55 (48.5–60)	54 (50–61.5)	0.921
Diagnosis (n)					
Breast	0	0	0	1	
Lung	5	1	3	3	
Gynecological	1	3	4	1	
Sarcoma	2	0	0	0	
Gastrointestinal	2	3	3	2	
Neck	0	2	1	0	
Prostate	2	0	0	2	
Pancreas	2	4	1	3	
Karnofsky performance status score	60 (50–70)	60 (50–70)	65 (55–80)	60 (50–65)	0.935
Daily opioid dose[a] at T0/T1 (mg/day)	45 (30–60)	55 (45–60)	55 (30–60)	35 (22.5–120)	0.578
Opioid medication (n)					0.969
Oxycodone SR	7	7	6	7	
Fentanyl patch	7	7	6	5	
Pain descriptors (n)					
Sharp	8	12	12	10	
Shooting	14	14	11	12	
Burning	5	5	5	6	
Classification of pain syndrome (n)					
Peripheral nerve syndrome due to retroperitoneal mass	2	6	1	3	
Radiculopathy due to vertebral lesion	8	4	2	5	
Brachial plexopathy	1	2	2	0	
Lumbosacral plexopathy	1	1	3	4	
Sacral plexopathy	2	1	4	0	

Values are median (interquartile range) or number

[a] Orally administered morphine equivalent

For this reason, we performed an evaluation of the analgesic effect of low-dose gabapentin–antidepressant combination in cancer pain with a neuropathic component.

Methods

Cancer patients diagnosed as having neuropathic pain that was not completely controlled with opioids analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) were enrolled in this study. Neuropathic pain was defined as pain associated with nerve compression or direct neoplastic invasion of the peripheral nerves or spinal cord. Patients with both sharp pain and burning or shooting pain (electric-shock-like) with or without allodynia were regarded as having neuropathic pain [8]. Approval from the local ethics committee was obtained, and if the pain was not completely controlled by opioids and NSAIDs, or the opioid dose was limited by side effects, oral informed consent was obtained and then gabapentin or/and imipramine were started after the first referral visit to our clinic.

In this randomized, controlled trial, cancer patients were allocated to one of four groups using computer-generated random numbers:

1. G400-I group: gabapentin 200 mg and imipramine 10 mg every 12 h orally.
2. G400 group: gabapentin 200 mg every 12 h orally.
3. G800 group: gabapentin 400 mg every 12 h orally.
4. I group: imipramine 10 mg every 12 h orally.

Previous 24-h average intensity of total pain was assessed on 0–10 numerical scales, and previous 24-h paroxysmal pain (shooting or lancinating pain) episodes were recorded [11]. Pain assessments were performed at the first visit (T0) and 7 days after the start of the medication (T1, the second visit). Opioid "rescue" doses were available as needed.

Table 2 Total pain score, daily paroxysmal pain episodes, previous 24-h opioid rescue dose, and adverse events

	G400-I (n = 14)	G400 (n = 14)	G800 (n = 12)	I (n = 12)	p value
Total pain score					
T0	7 (5–8)	7 (5–8)	6.5 (6–7)	7 (5–8)	0.970
T1	2 (2–3)	4.5 (3–6)*	4 (3–5)	5 (3–6.5)*	0.005
Pain episodes					
T0	4.5 (3–6)	4 (4–5)	5 (4–5)	4 (4–6)	0.749
T1	1 (0–2)†	3 (3–4)	3.5 (2.5–4.5)	4 (3–6)	<0.001
Opioid rescue dose at T1 (mg/day)	8 (0–25)	30 (25–30)*	25 (20–40)	25 (15–42.5)	0.008
Adverse events (n)					
Mild drowsiness	5	5	7	4	0.559
Mild dizziness	0	0	4	1	0.014
Severe dizziness	0	0	3	0	0.015
Nausea	1	1	1	1	0.999

Values are median (interquartile range) or number

* Different from the G400-I group ($p < 0.05$)

† Different from the other groups ($p < 0.05$)

[a] Oral morphine equivalent

NSAIDs already administered remained unchanged. No new drug was started during this period.

A pilot study of 20 cancer patients showed the mean [standard deviation (SD)] of the total pain score at T1 to be 2.3 (1.5), 4.2 (1.7), 4.0 (1.2), and 4.8 (1.0) in the G400-I, G400, G800, and I groups, respectively. We assumed that low-dose gabapentin–imipramine combination would improve the total pain score by at least 2° compared with gabapentin alone or imipramine alone. Thus, sample size of 9–14 was needed to show a difference of 2.0 (SD 1.2–1.5) in the total pain score at T1, with a significant level of 0.05 ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$). Data are presented as median (interquartile range). As Kolmogorov–Smirnov test was failed, data of patients' characteristics, daily opioid dose (oral morphine equivalent [12]), pain score, paroxysmal pain episodes, and previous 24-h opioid rescue dose at T1 (oral morphine equivalent [12]) were analyzed using the Kruskal–Wallis test followed by Dunn's method for multiple comparisons. Sex, opioid medication, and adverse event distributions were analyzed by the chi-squared test. A p value <0.05 was regarded as significant.

Results

Fifty-two patients with neuropathic pain were randomized into the G400-I (n = 14), G400 (n = 14), G800 (n = 12), and I (n = 12) groups, respectively. The four groups were comparable with respect to patient characteristics, daily opioid dose (oral morphine equivalents), and opioid medication (Table 1).

The four groups were comparable with respect to total pain score and daily paroxysmal pain episodes at T0 (Table 2). Low-dose gabapentin–imipramine combination significantly decreased total pain score and daily paroxysmal pain episodes (Table 2). Also, the combination significantly decreased the previous 24-h opioid rescue dose. Several patients developed mild adverse symptoms in the four groups, and three patients in the G800 group discontinued treatment due to adverse events (Table 2). As pain control was not sufficient in the G400, G800, and I groups, imipramine or gabapentin was prescribed at the second visit in order for the patients to take gabapentin 200 or 400 mg, and imipramine 10 mg every 12 h orally. At 7 days after the second visit, the median (interquartile range) of the total pain score and paroxysmal pain episodes was 2 (1–3) and 1 (0–1), respectively.

Discussion

Some cancer pain syndromes are less responsive to opioid analgesics than others [4–6, 13]. The pathophysiology involves multiple mechanisms. In particular, the presence of a neuropathic pathophysiology is associated with a less favourable outcome of opioid use [5, 8, 11, 13]. This observation indicates the need for nonopioid analgesics to be used in combination with opioids. Anticonvulsants and antidepressants are the most commonly used adjuvant analgesics in pain syndromes of cancer patients when a neuropathic pathophysiology is inferred from clinical findings [8, 11]. Thus, we planned to prescribe gabapentin

or/and imipramine instead of increasing the opioid dose at the first visit in patients in this study.

Presently, gabapentin is widely used to relieve pain, especially neuropathic pain. Several studies have shown that it is more effective than placebo in treating neuropathic pain caused by nonmalignant and malignant etiology [1, 7–10, 14–17]. In the experiences of nonmalignant etiology, gabapentin doses ranged from 600 to 3,600 mg/day. In the experiences of malignant etiology, doses ranged from 300 to 1,800 mg (median 1,200–1,800 mg). Also, gabapentin combined with morphine achieved better analgesia at lower doses of each drug than each drug alone [18]. However, we experienced many cancer patients reporting moderate to severe side effects in our daily clinical practice when doses >800 mg/day are used, leading to a discontinuation of gabapentin. Several experiments support the potential of combination pharmacotherapy for neuropathic pain [10, 19]. That is, combination pharmacotherapy could provide greater efficacy with lower doses and fewer adverse effects. A limitation of the methodology in this study was the failure to use placebo. However, the combination of low-dose gabapentin and imipramine more effectively alleviated cancer pain than gabapentin or imipramine alone. Furthermore, gabapentin 200 mg and imipramine 10 mg every 12 h were more effective than gabapentin 400 mg every 12 h. We thus believe that our results show the synergistic effectiveness of gabapentin–antidepressant combination pharmacotherapy in treating cancer-related neuropathic pain, without severe adverse effects.

In conclusion, low-dose gabapentin–antidepressant combination with opioids was effective in managing neuropathic cancer pain without severe adverse effects.

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今月のテーマ 神経因性疼痛

神経障害性疼痛の痛覚認知機構

Cortical mechanisms of neuropathic pain

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神経障害性疼痛でみられるアロデニアなどの異常な痛みは，最終的に脳で経験される不快な感覚情動体験である．そこでfMRIを用いてアロデニア部位に痛み刺激を加えた際および視覚刺激で痛みを仮想的に経験させた際の脳活動部位の調査研究を行った．仮想痛み刺激に対して，患者群では不快な感覚と同時に前帯状回と内側前頭前野の脳活動が検出された．神経障害性疼痛では慢性的な痛みに伴って神経系は可塑的変化を引き起こし，痛みが脳内のメカニズムだけでも引き起こされる状態になっていることを示すものと考えられた．

KEY WORDS 脳機能イメージング，神経可塑性，仮想痛み刺激

はじめに

慢性の痛みを引き起こす病態はさまざまなものがあるが，なかでも神経の損傷あるいは機能障害に起因する痛みはその特徴から難治性の経過をたどることが多く，神経障害性疼痛と呼ばれている．神経障害性疼痛はその特徴として神経の性格的変化である感作や可塑的な変化を引き起こし，安静時の痛みや侵害刺激によってより強い痛みが引き起こされる“痛覚過敏”（hyperalgesia）や通常痛みを引き起こさない程度の非侵害性の刺激が痛みを引き起こす“アロデニア”（allodynia：異痛症とも呼ぶ）を引き起こす．アロデニアは風が当たっても痛い，服の袖が触れても痛い，普通ではヒヤッとする程度の温度の金属を触れると痛いなど神経の機能変化が直接痛みの感覚に関与していることを示す症状であることから，神経障害性疼痛の症状として重要視されることが多い．

痛みには苦痛を伴うが，痛みは基本的には末梢からの刺激によって引き起こされることから，患者も治療者も痛みを訴える部分である組織に注目されがちである．しかし，痛みは主観的な感覚情動体験であり“頭（＝脳）”で経験するものである．実際，痛みの強さは患者の置かれた状況や環境などの要因によってしばしばその強度が変化する．持続性の強い神経障害性疼痛を有する患者でも，もっと別の強い痛みがあるときや何か別のことに意識が集中しているときなどは元来あった痛みの強さやそれに伴う苦痛は大きく変化する．そのため，痛みの評価は困難であるが少なくとも，痛みを脳で経験していれば何らかの脳活動として

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捉えることは可能でないかと考えられ，これまでSingle Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), functional Magneto-Resonance Imaging (fMRI), Magneto-Encephalogram (MEG) などさまざまな脳機能イメージング法を用いた研究が行われてきている．

そこで今回は，痛みに苛まされている患者さんにおける脳内の神経活動の変容について，その強い難治性の痛みを特徴とする神経障害性疼痛を例にとって諸家等の研究成果も踏まえた言及をしたい．

神経解剖学からみた脳内の痛みの伝達系

古典的な神経解剖学では，末梢に与えられた侵害刺激は主にAδ線維およびC線維の2種類の一次求心性線維の活動を引き起こし，脊髄後角細胞の一つである脊髄視床路細胞によって脳内に伝達されることが知られている．視床には多くの核が存在するが，痛みの伝達系においては，外側脊髄視床路（＝新脊髄視床路）が終末している腹側基底核群と前脊髄視床路（旧脊髄視床路）が終末している髄板内核群（主として外側中心核と束傍核）が重要な役割を果たしていることが知られている．前者は大脳皮質に主に投射する中継点であり，皮膚，内臓，筋，関節からの（識別性の）感覚に関与している．一方，後者は大脳辺縁系に投射し，痛みに関与する情動等に関与するとされている．脊髄視床路を含めて，これらの脳部位はペインマトリックスと呼ばれている（図1）[1]．

機械的痛み刺激と脳活動

先にも述べたように，神経障害性疼痛患者においては自発痛だけでなく痛覚過敏やアロデニアが患者を苛ましている要因になっていることが多い．これらの痛みは健常者で見られる生理的な痛みとは異なるメカニズムで引き起こされ，伝達されていると考えられており，近年の研究で後根神経節細胞や脊髄後角細胞レベルでの可塑的変化が関与しているのではないかと考えられている[2)~5)]．し

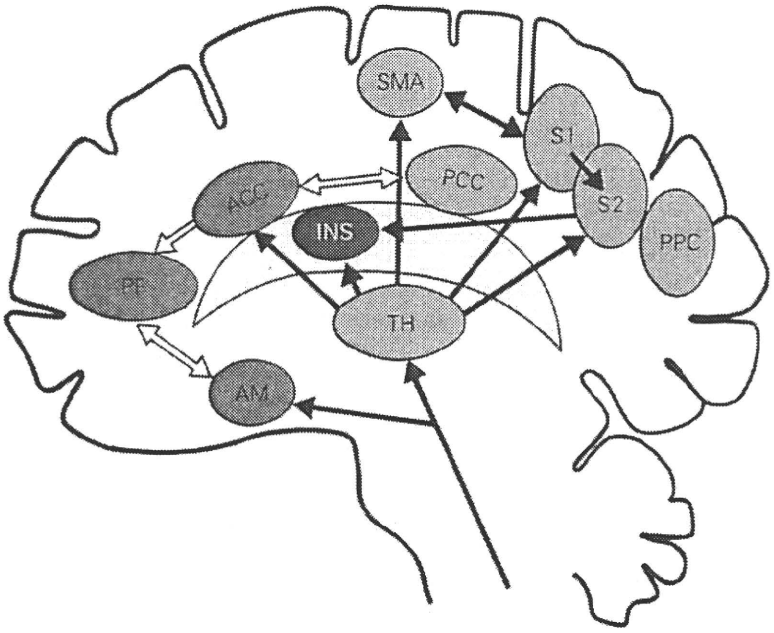

図1　脳内の痛覚情報伝達機構
脊髄を介して主に視床に伝達される痛覚情報はその識別を行う体性感覚野などに投射されると同時に島や情動に関与するとされる前帯状回に投射される．これらの脳部位の情報は脳内の各種ネットワークによって密接に連絡し合い，われわれは痛みを経験すると同時にその記憶を行っているものと考えられる．

かし，脊髄の異常に起因するものであっても最終的には脳が長く続く病的な痛みを経験していることを考えると，病的な痛みに応答する脳活動部位にも変化が起こっていることが示唆される．そこで，アロデニアを有する神経障害性疼患者に対して，健常者では痛みを引き起こさない強さのvon Frey フィラメント（11.5mN）を用いてアロデニアの部位を刺激した際に反応する脳部位についてｆMRIを用いて検討を行った．また，健常者において同じフィラメントで同部位を刺激した場合，および健常者でも痛みを引き起こす強さである490mNのvon Frey フィラメントの比較対象として行った．ｆMRIはGE社製SIGNA1.5Tを用いてスライス厚7mm，TR：4000mS，Echo Planner Imaging法で撮像した（各タスクの与えるタイミングに関しては図2，3を参照）．

その結果，患者群においてはVAS（Visual Analog Scale）において健常者群に侵害刺激を加えた際よりも強い痛みが観察されたにもかかわらず，末梢からの痛みの主な中枢である視床の活動性は検出されなかった．一方で，S1，S2，帯状回（主として後部帯状回）および運動野，補足運動野の活動が認められることが判った（図4，

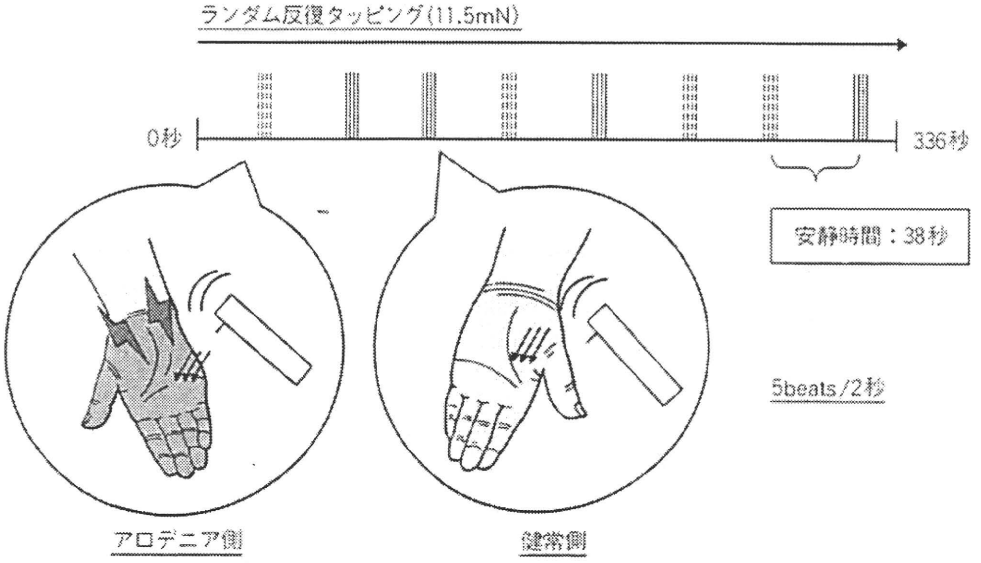

図2　アロデニア患者に対するｆMRIタスク（N＝8）

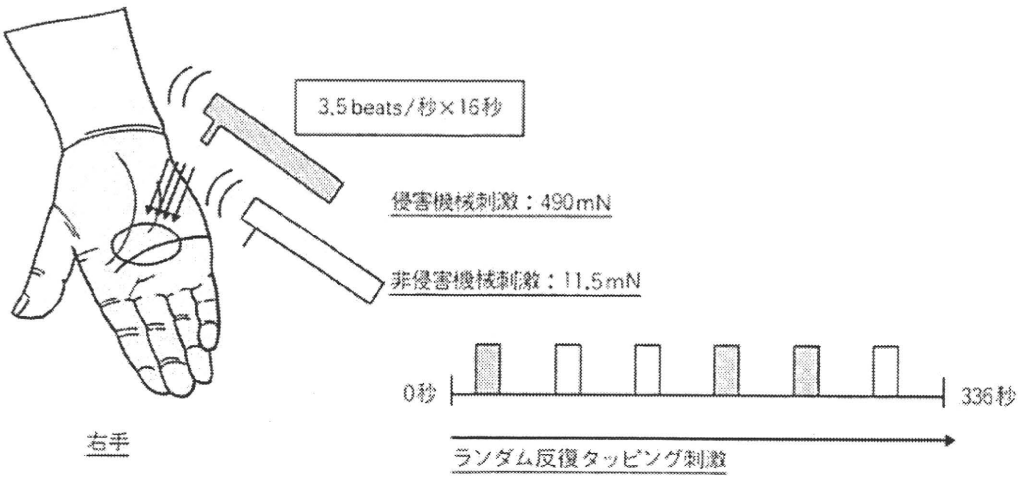

図3　健常者に対するｆMRIタスク（N＝12）

表1)[6]．他方，健常者に機械的侵害刺激を加えると，視床，S1，S2，帯状回，小脳における活動性の亢進が検出された（図5，表1）．Peyronらは筆者らのグループと類似の研究を行い報告しているが[7]，アロデニアを持つ患者の健側および患側に通常では痛みを感じない程度の機械的刺激を与えた際の脳活動についてはわれわれと類似の結論に至っている．

■■ 視床の活動について

1．視床の脳活動と慢性痛

視床は感覚の中枢と呼ばれ，痛覚の伝達においては先に述べた脊髄視床路が終末する部分でもあることから古くから痛み研究のターゲットとして注目されている部分であり，動物実験などによって部位別の詳細な分析が行われてきている．慢性痛における視床の役割については早期から注目さ

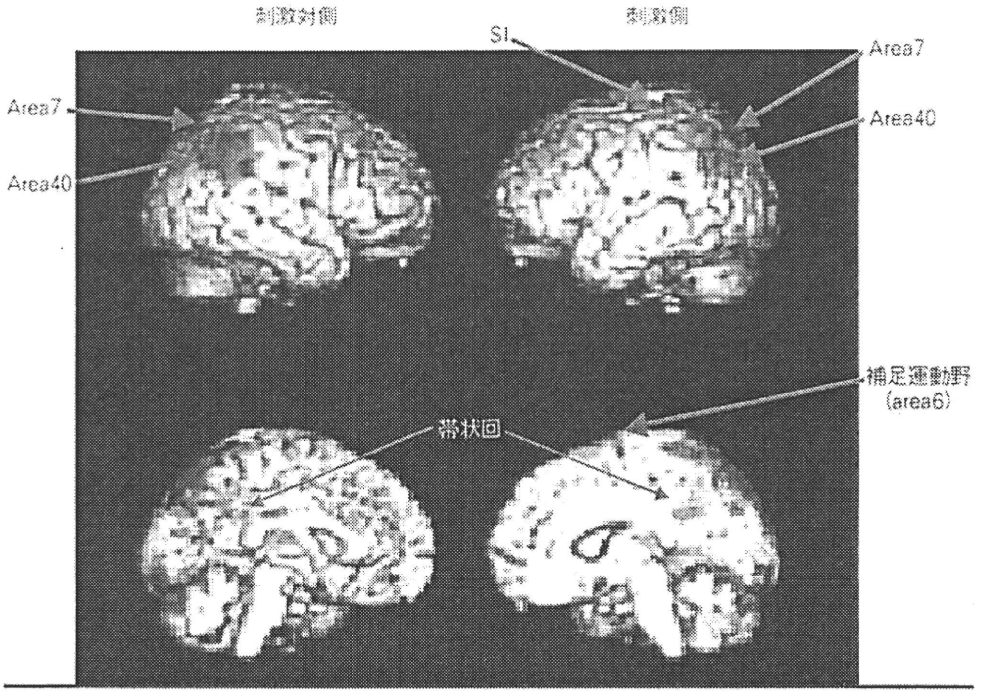

図4　アロデニア患者（N＝8）に機械的痛み刺激を加えたときの脳活動

表1　機械的痛みタスクを加えた際の脳活動部位の相違
健常者では脊髄視床路の終末する視床の活動が見られたが，アロデニア患者では検出されなかった．

	健常者群	アロデニア患者群
	侵害フィラメント	非侵害刺激
VAS	4.6（平均）	6.1（平均）
SI, SII	○	△
補足運動野（area 6）	—	○
運動野	△	○
帯状回	○	○
視床	○	−
小脳虫部	○	○

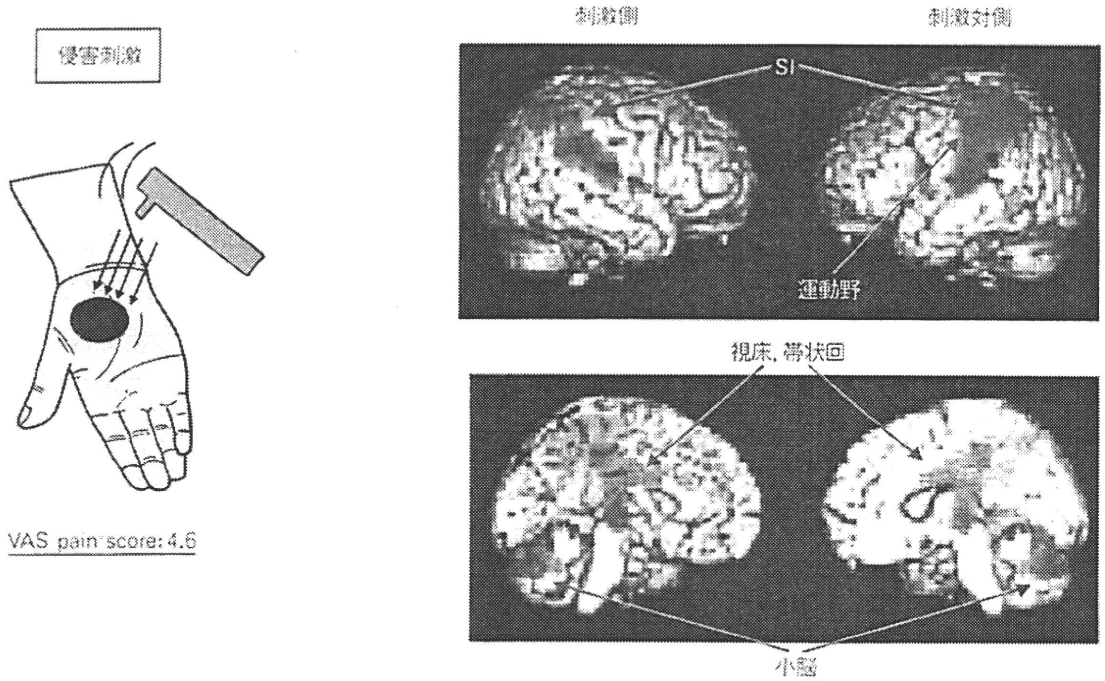

図5　健常者（N＝12）に機械的痛み刺激を加えたときの脳活動

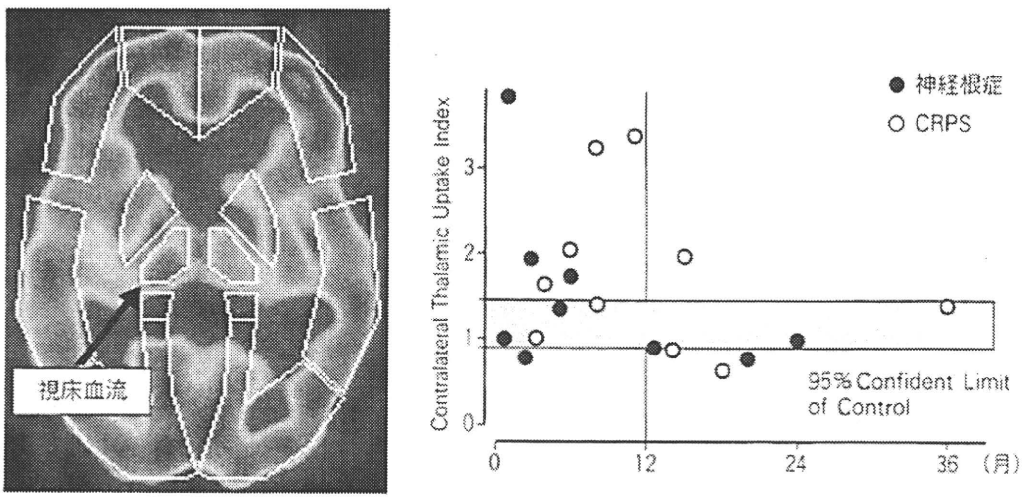

図6　病期と視床血流の変化

れており，脳機能イメージング法として早くから用いられてきたSingle Photon Emission Tomography（SPECT）やPositron Emission Tomography（PET）を用いた研究が行われてきている．

急性痛において視床の活動が引き起こされることが知られている一方で，慢性痛においては主に刺激伝達が引き起こされる対側の視床では活動がむしろ低下していることを示すデータが散見されている[8][9]．痛みと病期の関係についてSPECTの研究結果では急性期には亢進していた痛み部位と対側の視床活動は約1～2年程度で正常化し（図6）[10]，その後低下することも多いことが分かってきている[11]．前項で述べたようにわれわれの研究ではアロデニア患者においては機械的痛み刺激に対する視床の反応を検出することができなかったが，このような視床の機能的変化が少なからず影響していることが考えられ臨床的にも重要

な問題であると考えられる．この視床の血流低下は治療により，神経障害性疼痛の痛みが改善した際に改善するとの報告もみられる．中村らは視床血流の低下した慢性の帯状疱疹後に電気けいれん療法を施行し，症状の改善とともにSPECTによる視床血流の改善が出現することを報告している[12]．

このような変化の原因についての詳細は不明であるが，①持続的な慢性的な痛みが抑制系を活性化し，視床の機能を抑制している，あるいは②皮質感覚野が慢性的な視床からの入力によって持続的に易興奮性の状態に陥っており，わずかな視床からの痛み信号の入力に対しても痛みを認識する状態になっている，③視床におけるシナプス伝達が非常に効率化されたため血流亢進を要さない，④神経の興奮性とは無関係に慢性の病的な頭蓋内血流動態自体の変化が引き起こされたことで神経活動性と血流量の平衡関係が破綻した状態が引き起こされている，等が考えられるが慢性的な痛みでも対側視床の活動亢進がみられるとの報告も散見され，今後さらなる研究が必要と思われる．

2．動画（ビデオ）を用いた痛みの仮想体験に対する脳活動

慢性的にアロデニアのような痛みを有する神経障害性疼痛患者はしばしば，日常よりある痛みのため過度に患肢をかばったり，痛みから防御するような行動が観察され，同時に患肢の状態に関する関心は非常に強いことが多い．そこで，患部を直接触れて痛み刺激を加えるのではなく，ビデオ視認によって痛みを仮想的に体験させる研究を行い脳のどの部位が活動しているかを調べ，痛みの情動的要素について調べる研究を行った[13]．手にアロデニアを有する神経障害性疼痛患者が筆で痛みのある手掌を触られているビデオを視認した場合，不快な感覚体験をすると同時に健常者群と違って，前帯状回と内側前頭前野の活動が亢進することがわかった（図7，8）．前帯状回は健常者が「痛そうな画像」を見たときに賦活することがすでに示されており[14][15]，アロデニア患者においてもビデオ視認によって引き起こされた不快情動を反映したものであることが推察される．前頭前野は記憶の形成に重要な役割を果たすほか，うつ病などにも関係していることが知られている．この部位は，慢性腰痛の患者において痛みを経験した際にも活動することが報告されており，記憶という点を介して痛みの慢性化形成とその維持に関係していることが推察される．類似の実験系において，誰でも一度は経験したことがあると考えられる注射針を刺されることを健常者にビデオ提示した際のfMRI研究の結果では，著明な不快感の出現はなく，脳活動は主として島皮質の前方の活動性が検出された一方で前頭前野の活動は検出されなかった[16]．このことは，痛みが病的な状態になった場合と単に過去の痛みの経験を想起させただけのものとは異なる脳内メカニズムが関与しているものと考えられた．

また，アロデニアを有する神経障害性疼痛患者では実際の機械的刺激に対して視床の活動が低下している報告があることなどを考慮すると，慢性痛を有する患者では痛みを脳が記憶し，再現し，繰り返して経験するような状態になっているのではないかと考えられる．実際，神経障害性疼痛に限らず慢性的に痛みを有する患者においては，痛みに対する破局化傾向を示すことが多いことが最近強調されてきている．いつも痛みのことを心配していたり，自分の痛みは悪くなると思ったり，治らないと思ったりなどの傾向が高い場合それ自体が患者を煩わせる要素になるということもある．われわれの自験例では，脊髄損傷後に下半身の完全麻痺とともに氷につけられたような慢性的な強い痛みが生じた薬物治療抵抗性の症例を経験しているが，車椅子スポーツ選手として復帰したのをきっかけに痛みの苦渋から開放された症例を経験している．この患者においては，痛みそれ自体は変わらないが，痛みによる苦痛は改善したと述べている．このことは脳内における認知機構の中で，不快な情動体験としての痛みのほうが，識別的な感覚体験としての痛みよりも苦痛に関与し，患者の苦しみという側面からはより重要な問題である

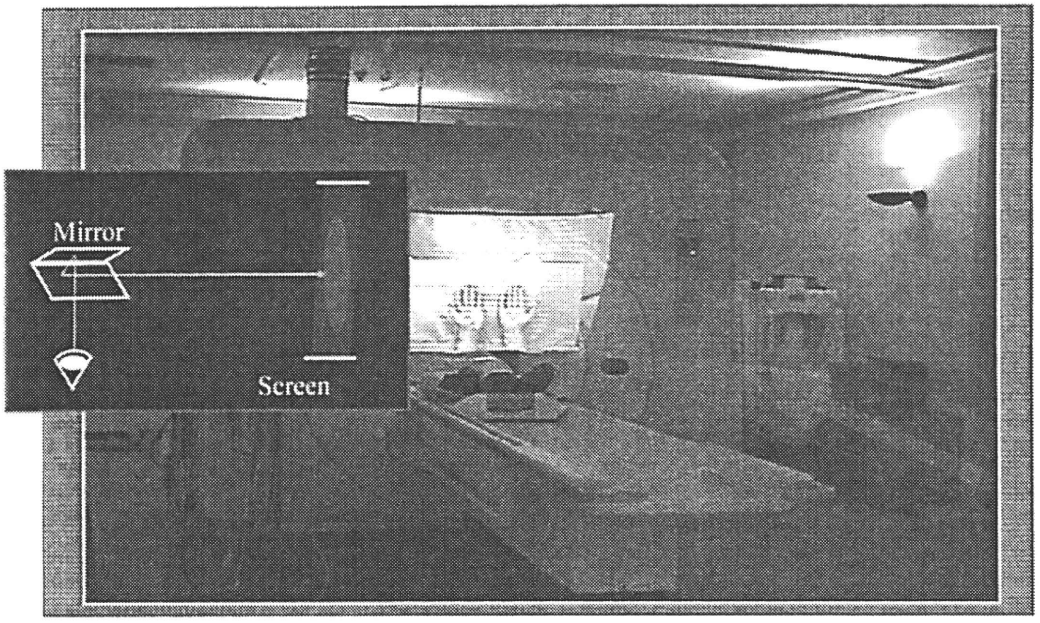

図7　ビデオ提示をタスクにしたfMRI撮像
被験者はスクリーンに投射されたビデオを脳機能タスクとして視認する．その際の脳活動をEPI法にてMRIで撮像する．

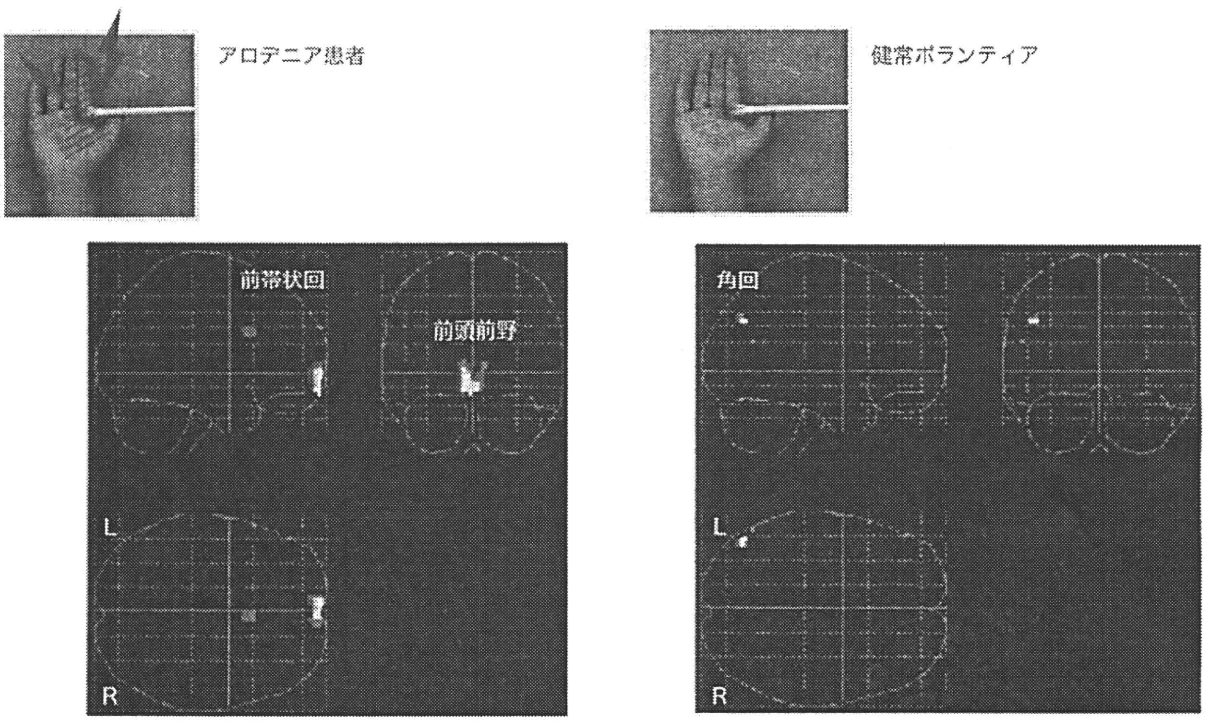

図8　仮想痛みビデオを観たときの脳反応

ことが考えられる．

これらのことを考慮すると，今後の慢性痛の治療においては，痛みによる不快な記憶は止めようがないけれども，これらのネガティブな経験の繰り返しをさせない，あるいは問題にならないようにさせるような工夫によって，患者の人間としてのアメニティを向上させることが最も重要になるものと考えられる．

まとめ

・機械的な刺激もビデオによる疑似痛み経験もアロデニア患者においてはペインマトリックスに脳活動が観察された.

・アロデニア患者において疑似痛み経験でも強い不快感が出現したことは, 神経因性疼痛の痛みの維持に脳内での経験の繰り返しが大きなウエイトを占めていることが推察された.

・今後は脊髄一脳の痛み伝達系についても研究を進める必要があると考えられる.

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