

Brain metabolic changes associated with predisposition to onset of major depressive disorder and adjustment disorder in cancer patients –A preliminary PET study

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Abstract

Objectives: To explore neurobiological risk factors for major depressive disorder (MDD) and adjustment disorder in cancer patients by examining regional brain metabolism before psychiatric manifestation using positron emission tomography and by prospectively observing depressive and anxiety symptoms.

Method: Cancer patients who showed no psychiatric symptoms when they underwent ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) were followed up for one year using the Hospital Anxiety and Depression Scale (HADS). Fourteen patients who showed high HADS scores and 14 patients who showed low HADS scores were assessed by a psychiatrist 2 years after the PET scan and grouped into the deterioration group ($n = 10$) and the no-change group ($n = 9$). ¹⁸F-FDG PET images were analyzed to examine the difference in local brain glucose metabolism between the two groups.

Results: The deterioration group showed a decreased glucose metabolism in the right medial frontal gyrus (BA6) and an increased glucose metabolism in the right posterior cingulate (BA29), right anterior cingulate (BA25), left subcallosal gyrus (BA25), and left caudate compared with the no-change group.

Conclusion: Cancer patients who later developed MDD or adjustment disorder showed regional brain metabolic changes. These regions may be associated with vulnerability to the onset of MDD or adjustment disorder in cancer patients.

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1. Introduction

Cancer patients often suffer from psychiatric comorbidities, thereby significantly decreasing their quality of life. Derogatis et al. (1983) reported that 47% of cancer patients have some psychiatric disorders. Among them, 68% had adjustment disorder, approximately 13% depression, and 8% delirium. In a different study, 20–45% of

cancer patients have been shown to suffer from depression (Katon and Sullivan, 1990). In a survey with terminally ill cancer patients in Japan (Akechi et al., 2004), 16.3% and 6.7% of them were diagnosed as having adjustment disorder and major depression, respectively. The incidence rate of depression in cancer patients seemingly depends on the tumor-affected area. Higher incidence rates are observed in pancreatic cancer (50%) and pharyngeal cancer (22–40%), and lower incidence rates in gastric cancer (11%) and leukemia (1.5%) (McDaniel et al., 1995).

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Considering the established efficacy of antidepressants in cancer patients with depression (Massie and Holland, 1990) as well as of psychological interventions for improving the emotional state and quality of life of cancer patients (Fawzy et al., 1993; Goodwin et al., 2001), it is essential to assess the psychiatric state of these patients and intervene, if necessary, at earlier stages. However, only 0.5–3% of cancer patients are referred to psychiatrists (Uchitomi et al., 1993), and many cancer patients with adjustment disorder or depression are presumably overlooked. The prediction, early detection and intervention of depressive and anxiety symptoms would therefore improve the quality of treatment of cancer patients.

The mechanism underlying the development of psychiatric symptoms in cancer patients has not been fully elucidated. Some possible psychosocial factors have been proposed, such as psychological burden and coping with it, and burden from invasive treatments such as chemotherapy (Petty and Noyes, 1981). Putative risk factors for depression in this population also include social isolation, recent losses, a tendency toward pessimism, the presence of pain, socioeconomic pressures, the diagnosis of alcoholism or substance abuse, a history of mood disorders or suicide attempts (McDaniel et al., 1995). Factors like younger age, longer education, lower performance status, severer fatigue, being a burden to others, and loss of independence and dignity are also associated with adjustment disorders and/or major depression in terminally ill cancer patients (Akechi et al., 2004).

By contrast, relatively few studies have been conducted for biological factors potentially predisposing the same population to psychiatric conditions. Although some biological abnormalities such as an altered immune system (e.g., natural killer cell activity) (Levy et al., 1985, 1987) and an increased hypothalamus–pituitary–adrenal (HPA) axis activity (Evans et al., 1986) have been suggested as factors associated with mental distress, recent advances in neuroimaging techniques have led to some interesting data concerning alterations in brain structures and functions in cancer patients with psychiatric symptoms. In a structural MRI study, Nakano et al. (2002) reported that having distressing cancer-related recollections is associated with a smaller left hippocampal volume in survivors of breast cancer, but first major depressive episodes after cancer diagnosis in female cancer survivors do not appear to be associated with hippocampal volume (Inagaki et al., 2004). Yoshikawa et al. (2006) also reported that a smaller amygdala volume is associated with a first minor and/or major depressive episode after cancer diagnosis. A preliminary PET study (Tashiro et al., 2001) showed that cancer patients with high Zung's Self-rating Depression Scale (SDS) scores showed a lower metabolism in the bilateral frontal cortices, bilateral anteroposterior cingulate gyri, bilateral temporoparietal cortices, insula, anterior temporal cortex and basal ganglia than patients with benign tumor. In all these studies, the brain structure and metabolism after the emergence of psychiatric symptoms were

assessed. However, the psychiatrically premorbid examination of the same aspect remains to be performed.

In major depression in the general population, local brain metabolism is reportedly decreased in the prefrontal lobe, dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex, subgenual prefrontal cortex (subgenual PFC), basal ganglia and temporoparietal cortex (Baxter et al., 1989; Bench et al., 1992; Drevets et al., 1997), and increased in the orbital cortex, amygdala and thalamus (Drevets et al., 1992; Price et al., 1996). Mayberg et al. (1999) reported that depressed patients exhibit a decreased metabolism in the subgenual cingulate and an increased metabolism in the DLPFC, anterior cingulate and posterior cingulate after remission. Although some brain areas that have been shown to have a lower metabolism in major depressive episode overlap between cancer and noncancer patients, it remains unclear whether these two populations share the same biological vulnerability to and the same pathophysiology of depressive symptomatology.

The objectives of the present study were to investigate the onset of major depressive disorder (MDD) and adjustment disorder in cancer patients prospectively and to explore the mechanisms underlying its onset by brain imaging, in the search for neurobiological changes associated with vulnerability to developing MDD or its milder form, adjustment disorder.

2. Subjects and methods

2.1. Subjects

One hundred and seventeen outpatients and inpatients of the Department of Gunma University Hospital in Japan consented to participate in this psychooncological study. The participants were patients who were scheduled to undergo head or whole-body ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) on a clinically routine basis to detect cancer metastasis after being diagnosed as having malignant cancer or to monitor the therapeutic process after treatment for malignant cancer.

All the patients who consented to participate in this study were assessed by a psychiatrist for psychiatric symptoms and also submitted a self-completed report instrument, the Japanese version of Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983; Kitamura, 1993) after the PET scan. The same questionnaire was sent 3, 6, and 12 months after the PET scan, and 78, 61, and 46 patients responded, respectively. We used 14 as the HADS cut-off score for grouping patients for psychiatric screening. Previous studies showed that HADS scores of 13 and higher often indicate adjustment disorder or MDD (Hosaka et al., 1999); HADS scores of 13 and higher have a 75% sensitivity and 15 and higher have a 90% positive predictive value (Razavi et al., 1990) for MDD and adjustment disorder. Thus, it is appropriate that we interpreted HADS scores of 14 and higher to indicate a high possibility for the psychiatric diagnosis of MDD or adjustment disorder for screening.

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