IV. 5. Regional Metabolic Abnormality in Brains of Patients with Cancer

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Introduction

Imaging technique using positron emission tomography and 18F-fluoro-deoxyglucose (FDG PET) has been utilized for a few decades as a useful tool to detect malignant tumors at early stages, as well as for differentiation from benign diseases 1,2. FDG PET has been also useful for evaluation of a variety of neuropsychiatric disorders such as depression 3,4 and obsessive compulsive disorder 5 by examining regional cerebral metabolic rate of glucose (rCMRglu). So far, it does not seem that this technique has been applied for evaluation of neuropsychiatric abnormalities of cancer patients before. Functional brain imaging techniques might be helpful in evaluating neuropsychiatric problems in cancer patients, too.

We previously reported the results of preliminary examination on the regional cerebral abnormalities of glucose metabolism in patients with cancer 6-7,8). In the previous reports, we reported that cancer patients manifest regional hypometabolism in the prefrontal cortex and limbic system 7,8). The metabolic decline seemed to be associated with pain and types of disclosure to patients 7). The present report is trying to supplement detailed description of this tendency.

Materials and Methods

Subjects were 19 cancer patients who were studied with FDG PET at the Cyclotron and Radioisotope Center (CYRIC), Tohoku University during the period of 1995 to 1997 2). The 19 cancer patients over 40 years old, who fulfilled the two following criteria, were selected from the data base: (1) absence of focal signs of brain metastasis and cerebrovascular diseases in MRI or CT and PET, and (2) absence of invasive treatments such as surgery, chemotherapy and radiotherapy before PET examination. The 19 patients were diagnosed with malignant diseases of various organs as follows: twelve patients as lung cancer (including one small cell lung cancer), three as malignant mediastinal tumor, two as
esophageal cancer, one as malignant lymphoma and the other as gastric cancer (mean age +/- S.D., 65 +/- 10, range 44 to 84, two women and 17 men). Patients were scanned approximately 30 min after injection of FDG taking about 30 min. Seventeen patients in the control group had ophthalmopathy such as optic neuritis and macula hole (mean age +/- S.D., 64 +/- 9, range 48 to 78, seven women and 10 men). The study protocol was approved by the Ethics Committee for clinical Research of Tohoku University and informed consent for the all examinations for the study was obtained in advance from each patient.

Clinical data and subgroups:

Clinical information of each cancer patient was retrospectively collected from medical charts. Pain, sleep disturbance, appetite loss, and types of disclosure were graded according to the following criteria.

Pain: (-) no pain (n=13), (+) mild pain controlled by non-steroidal anti-inflammatory drugs (NSAIDs)(n=3), and (++) severe pain which required narcotics (morphine and opiates)(n=3).

Sleep disturbance: (-) no sleep disturbances (n=15), (+) mild sleep disturbances successfully controlled by a hypnotic (n=2), and (++) moderate to severe sleep disturbances which required more than two hypnotics for control (n=2). Four patients manifested sleep disturbances.

Amount of hospital meals taken by each patient was reviewed for 5 days prior to PET examination: (-) when a patient ate more than 90 percent of meals served for the 5 days (n=15), (+) more than 50 percent (n=3), and (++) less than 50 percent (n=1).

Types of disclosure of malignant nature of the disease: 1) complete disclosure (CD) group (n=3), already informed of the malignant nature before PET examination, 2) possible malignancy (PM) group (n=9), being informed of malignant findings possibly detected by PET examination, 3) non-disclosure (ND) group (n=3), intentionally given a false benign diagnosis by doctors at the request of patients' families, and 4) no information group, in case no information was found in the medical charts (n=4), omitted from the comparison.

We attempted preliminary statistical evaluation for the regional metabolic rate ratios among subgroups graded for clinical information using Mann-Whitney's U-test due to small sample size. Plasma glucose concentrations of subjects were within normal ranges (99.8 +/- 6.0mg/dL).

Results

Statistical analysis using SPM96 identified several regions with decreased regional metabolic rate ratios in cancer patients compared to the control. The metabolic reduction was found in the prefrontal cortex and limbic and paralimbic structures.
The severe pain group showed a trend for decreased regional metabolism in the anterior cingulate gyrus compared to other sub-groups. Similar trend was observed in the striatum, too, but both were insignificant by Mann-Whitney's test (Figure 1). As to the types of disclosure, CD group manifested relatively increased metabolic rate ratios (figure 2).

The regional metabolic rate ratio in the anterior cingulate gyrus of the appetite loss group showed a trend for higher metabolism but the difference was not significant. No significant difference was detected between the groups with and without metastasis.

Discussion

In an attempt to normalize the influence of stress due to hospitalization, the authors selected benign disease in-patients as the control group. This comparison was expected to highlight the neuropsychiatric problems of cancer. In the present study, no patients had anticancer therapies before the PET study. Derogatis et al. reported that 47 percent of cancer patients met the DSM-III criteria\(^9\). Minagawa et al. reported that 53.7 percent of terminally-ill cancer patients met DSM-III-R criteria\(^10\). According to previous studies, neuropsychiatric problems of cancer patients could be induced by both psychological factors and invasive treatments\(^11\). Etiological factors which possibly cause resultant psychiatric abnormalities could be classified grossly as follows: 1) psychological response, 2) biological effects due to existence of cancer, 3) biological effect due to treatments, and 4) pain.

The authors preliminarily examined the correlation between the metabolic rate ratios and the degrees of sleep disturbances and appetite loss, both of which constitute chief physical symptoms of depression. The results suggest that these physical symptoms are not appropriate for this study because they could be caused by malignant disease itself. Concerning the grade of pain, the severe pain group showed a trend for lower metabolism in the anterior cingulate gyri compared to the other sub-groups. Our result could be interpreted in association with alteration in the threshold of pain sensation due to the use of narcotics\(^12,13\) (Figure 2).

As to types of disclosure, in Japan, some doctors still hesitate to tell truth to their patients. The rate of complete disclosure might be lower in Japan than in Western countries as demonstrated in the present study (3/19), too, as well as in previous reports\(^14,15\). The author examined whether any regional metabolic differences could be detected among groups with different disclosure types.

Conclusion

In conclusion, the brain of cancer patients showed a clearly different metabolic pattern compared to controls, showing declined metabolism in the limbic system. This abnormality seems to be difficult to explain by physical factors. Since the brain metabolic pattern resembles that of major depression, more association with psychiatric or psychological factors should be examined. Due to the small size of patient groups, intra-group comparisons did
not clarify the causes and effects. More studies are necessary to clarify the relationship. In future, evaluation of cerebral glucose metabolism with PET may offer an objective method to assess psychological and neurological problems of cancer patients.

References


Figure 1. Type of Disclosure and Regional Metabolic Rate Ratios in Brain of Cancer Patients.
Result of intra-group comparison based on types of disclosure. Abbreviations: ACG= anterior cingulate gyrus, OF= orbitofrontal cortex, ST= striatum, HPH= hippocampus and parahippocampal gyrus, C= control group, CD= complete disclosure group, PM= possible malignancy group, ND= non-disclosure group. Symbols: p<0.05: compared between CD and PM groups by Mann-Whitney's test.
Figure 2. Degree of Pain and Regional Metabolic Rate Ratios in Brain of Cancer Patients.
Result of intra-group comparison based on degree of pain. Abbreviations: ACG= anterior cingulate gyrus, OF= orbitofrontal cortex, ST= striatum, HPH= hippocampus and parahippocampal gyrus, C= control group, (++) moderate to severe pain, (+) mild pain, and (-) no pain. Symbols: p<0.05: compared between CD and PM groups by Mann-Whitney's test.