Original Article

Preliminary Study of Brain Glucose Metabolism Changes in Patients with Lung Cancer of Different Histological Types

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Abstract

Background: Cerebral glucose metabolism changes are always observed in patients suffering from malignant tumors. This preliminary study aimed to investigate the brain glucose metabolism changes in patients with lung cancer of different histological types.

Methods: One hundred and twenty patients with primary untreated lung cancer, who visited People's Hospital of Zhengzhou University from February 2012 to July 2013, were divided into three groups based on histological types confirmed by biopsy or surgical pathology, which included adenocarcinoma (52 cases), squamous cell carcinoma (43 cases), and small-cell carcinoma (25 cases). The whole body 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) of these cases was retrospectively studied. The brain PET data of three groups were analyzed individually using statistical parametric maps (SPM) software, with 50 age-matched and gender-matched healthy controls for comparison.

Results: The brain resting glucose metabolism in all three lung cancer groups showed regional cerebral metabolic reduction. The hypo-metabolic cerebral regions were mainly distributed at the left superior and middle frontal, bilateral superior and middle temporal and inferior and middle temporal gyrus. Besides, the hypo-metabolic regions were also found in the right inferior parietal lobule and hippocampus in the small-cell carcinoma group. The area of the total hypo-metabolic cerebral regions in the small-cell carcinoma group (total voxel value 3255) was larger than those in the adenocarcinoma group (total voxel value 1217) and squamous cell carcinoma group (total voxel value 1292).

Conclusions: The brain resting glucose metabolism in patients with lung cancer shows regional cerebral metabolic reduction and the brain hypo-metabolic changes are related to the histological types of lung cancer.

Key words: 18F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography; Brain Glucose Metabolism; Lung Cancer; Statistical Parametric Mapping

Introduction

Lung cancer is one of the most common malignant tumors, and the patients with lung cancer usually have a high rate of depression because of various factors.[1-4] Studies of cerebral glucose metabolism changes in patients with malignant tumors detected by brain positron emission tomography (PET)/computed tomography (CT) imaging are helpful to reveal the characteristics and generation mechanism of mental disorders in these patients. Some studies have shown that there are widespread early changes of cerebral metabolic abnormalities in patients with malignant tumors,[5,6] and a few studies have also shown that different types of tumors show different cerebral metabolic changes.[7] However, particular cerebral metabolic changes for the tumor at same site but with different histological types have not been reported at home and abroad.[8,9] This preliminary study aimed to provide some help for brain biological mechanisms, clinical diagnosis, and treatment of lung cancer patients with depression or affective disorders.

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Methods

Subjects

The patients with primary lung cancer, who underwent whole-body PET-CT examination in PET-CT Center of People's Hospital of Zhengzhou University from February 2012 to July 2013, were analyzed retrospectively. The inclusion criteria were as follows: (1) the primary lung cancer was confirmed by histopathology report of biopsy or surgical specimens, and the patients were untreated; (2) the patients had no imaging features suggestive of metastatic brain tumors and/or other brain diseases; (3) no past medical or family history of cerebrovascular accident, epilepsy, traumatic brain injury and brain surgery, hyperthyroidism,

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diabetes and other metabolic diseases, and mental illness. Eventually, 120 patients who met all of the above criteria were enrolled in this study, and were divided into three groups on the basis of histological types: squamous cell carcinoma in 43 patients, adenocarcinoma in 52 patients, and small-cell carcinoma in 25 patients. All the selected patients were right handed. Fifty age-matched and gender-matched healthy controls were recruited from the local community who were also right handed. The study protocol was approved by the Ethics Committee of Clinical Research of Zhengzhou University, and all patients provided the informed consents.

18F-fluorodeoxyglucose positron emission tomography scanning

18F-fluorodeoxyglucose (18F-FDG) PET imaging was obtained using GE Discovery™ VCT PET/CT set (GE Medical Systems, USA) in PET-CT Center of People's Hospital of Zhengzhou University. 18F-FDG was synthesized by medical cyclotron GE Minitrace and FDG automatic synthesis device (GE Medical Systems, USA), and quality assurance tests were performed. Before the examination, all patients were required to fast for at least 6 hours and the fasting blood glucose level of each patient was <6.1 mmol/L. 18F-FDG was injected in an intravenous bolus, the dose was 5.55 MBq/kg. After the injection, each subject remained in a resting state in a quiet environment for a 50-minute-uptake period. PET collection was performed using the emission, transmission alternate mode with the transaxial spatial resolution of 3.8 mm at full-width-half-maximum (FWHM). The axial field of view of the scanner was 200-mm-long. The brain scans were performed after whole body scans. The brain acquisition time was 10 minutes. Brain PET/CT scan parameters: Voltage 120 kV, current 240 mA, thickness 5 mm, and the images were reconstructed to transverse, sagittal and coronal images by iterative method.

Statistical analysis

The brain PET images were converted into Analyze 7 image data format using statistical parametric map 8 (SPM8, Wellcome Department of Imaging Neuroscience, London, UK) on the Talairach brain atlas with a voxel size of $2 \times 2 \times 2$ mm^3. Then the images were spatially normalized to the space coordinates with Talairach brain atlas. The normalized images were smoothed with an isotropic Gaussian kernel of 8 mm FWHM. A two-sample *t*-test of voxel-based statistical analysis on these cerebral FDG-PET images was performed, respectively, between each lung cancer patient group and the control group. The hypo-metabolic areas were identified by xjView software (Stanford University, CA, USA), and the voxel value of each brain area was calculated. Randomized block design analysis of variance was used to measure the voxel values of abnormal activation cerebral regions of the three study groups. Total voxel values of abnormal activation cerebral regions of each two study group were measured respectively by two-sample *t*-test. The age of every group was expressed as mean ± standard deviation (SD). All clinical data were analyzed by SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The Fallout Edition Wanderers corrected $P < 0.05$ was considered as statistically significant.[10]

Results

Demographic information

There were 30 males and 13 females in squamous cell carcinoma group (mean age of 54.37 ± 10.51 years old); 37 males, 15 females in adenocarcinoma group (mean age of 55.12 ± 11.34 years old); and 17 males and 8 females in small-cell carcinoma group (mean age of 54.15 ± 12.87 years old). The control group included 37 males and 13 females (mean age of 54.97 ± 12.44 years old). There was no statistically significant difference of gender ($\chi^2 = 0.36$, $P = 0.95$) and age ($F = 3.12$; $P > 0.05$) between four groups.

Data analysis

Compared with the healthy controls, the brain PET imaging in all three lung cancer groups showed a relative reduction of regional cerebral resting glucose metabolism ($P < 0.05$). The hypo-metabolic cerebral regions were mainly distributed at the left superior-middle frontal gyrus, bilateral superior-middle temporal gyrus or/and inferior-middle temporal gyrus. Besides, the hypo-metabolic regions were also found in the right inferior parietal lobule and hippocampus in the small-cell carcinoma group [Figure 1]. And there were statistically significant differences among the voxel values in abnormal activation cerebral regions of three lung cancer groups ($F = 87.53$, $P < 0.01$). The area of total

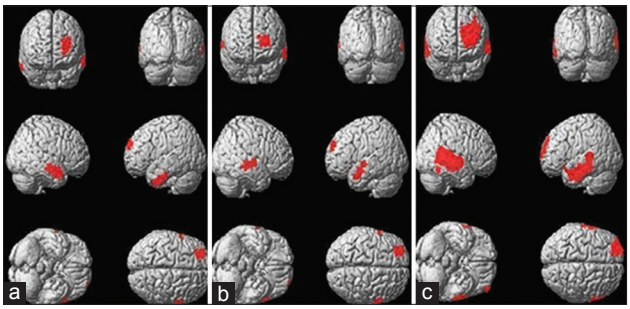

Figure 1: The visualization of statistical parametric map (SPM) in the patients with lung cancer. (a) The visualization of SPM in patients with lung adenocarcinoma. The cerebral regions of reduced brain glucose metabolism (red areas) were distributed in the left middle and inferior temporal gyrus, right middle, and inferior temporal gyrus and left middle and superior frontal gyrus. Total voxel value of the involved regions was 1217. (b) The visualization of SPM in patients with lung squamous cell carcinoma. The cerebral regions of reduced brain glucose metabolism (red areas) were distributed in the left middle and inferior temporal gyrus, right middle and superior temporal gyrus and the left middle and superior frontal gyrus. Total voxel value of the involved regions was 1292. (c) The visualization of SPM in patients with lung small-cell carcinoma. The cerebral regions of reduced brain glucose metabolism (red areas) were distributed in the left superior middle and inferior temporal gyrus, left middle and superior frontal gyrus, right middle and superior temporal gyrus, right inferior parietal gyrus and the right hippocampus. Total voxel value of the involved regions was 3255.

hypo-metabolic cerebral regions in the small-cell carcinoma group (total voxel value of 3255) was significantly larger than those in the adenocarcinoma group (total voxel value of 1217, $t = 14.33$, $P < 0.01$) and the squamous cell carcinoma group (total voxel value of 1292, $t = 10.07$, $P < 0.01$). And there was no statistically significant difference of abnormal activation cerebral regions between adenocarcinoma and the squamous cell carcinoma groups ($t = 0.764$, $P = 0.525$) [Table 1].

Discussion

In this study, the brain PET imaging in the three groups of patients with adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma showed not only common features, but also a difference in the cerebral resting glucose metabolism. Each group demonstrated reduced brain metabolism in some cerebral regions, which were related to mood regulation.[11] These findings were also similar to those changes seen in patients with primary depression.[12,13] It meant that patients with any histological type of lung cancer may have risk of suffering from depression or depressive tendency. In addition, the brain metabolic changes in the small-cell carcinoma group were much severer than those in the adenocarcinoma and squamous cell carcinoma groups. It can be concluded that the resting brain glucose metabolic changes in the patients with lung cancer are related to the histological types of tumor cells. This also implied that patients with lung cancer of different histological types may show the difference in risk of suffering from depression and may manifest different depressive symptoms.

In our study, there were two characteristics in the brain resting glucose metabolic changes in small-cell carcinoma. One was that the distribution of the hypo-metabolic regions in small-cell carcinoma was wider than those in the adenocarcinoma and squamous cell carcinoma. Besides the involvement of some gyri of the left frontal and the bilateral temporal lobe, the hypo-metabolic cerebral regions in the right inferior parietal lobule and hippocampus were also demonstrated in the small-cell carcinoma group. The metabolic reduction in inferior parietal lobule was mentioned in previous researches on other malignant tumors.[14] But, the hippocampal metabolic reduction has not been reported till date. Maybe this is one of the characteristics of brain glucose metabolism in small-cell lung cancer patients. But it needs to be further confirmed by more studies. Another characteristic in the small-cell carcinoma group was that its area of the total hypo-metabolic regions was significantly larger than those in the adenocarcinoma and squamous cell carcinoma groups. These brain metabolic characteristics could imply that small-cell lung carcinoma may cause severer brain damage. This was just corresponding to some results of clinical researches that patients with small-cell lung carcinoma had a higher depression incidence compared with other lung cancer patients.[7] The underlying reasons for these findings may be multifarious, including tumor biological characteristics, course of the disease, tumor stage, treatment history and even sociology and mental psychology.[15-17] In this study, the majority of these factors, such as course of the disease, tumor stage, and treatment history, have been controlled in this set. Now, we just tried to preliminarily analyze the point of biological characteristics of small-cell lung carcinoma. First, it may be related to the malignant degrees and growth pattern of tumor. The malignant degree of small-cell lung carcinoma is usually much higher than those of squamous cell carcinoma and adenocarcinoma. The tumor cell invades the lymph and blood system very easily at the early stage of this disease. Accordingly, the function impairment to brain and other organs deriving from small-cell lung carcinoma occurs earlier and severe. Second, it may be related to the specific neuroendocrine function of small-cell lung carcinoma. Small-cell lung carcinoma is the most important kind of neuroendocrine tumors of ectopic adrenocorticotropic hormone (ACTH) secretion. ACTH could lead to a reduction in synthesis of central 5-hydroxytryptamine (5-HT) and noradrenaline (NE), and the reduced 5-HT and NE in the central nervous system is closely related to depression.[18-20] This could also be verified by some results from other researches on patients with pancreatic neuroendocrine carcinoma.[7] In this study, the involvement of the hippocampus in patients with small-cell lung cancer can be explained by following mechanism. Hippocampus has many functional connections with nearly 30% of the brain regions.[21] There is abundance of glucocorticoid receptors in the hippocampus, and the increased blood cortisol level could easily result in the damage of hippocampal neurons, which consequently cause a variety of obstacles on learning, memory, and emotion. Many neuroimaging studies have confirmed that cancer patients and patients with depression both have hippocampal atrophy and dysfunction.[16,22,23]

As a preliminary retrospective analysis, this study had some limitations. First, the sample size was not large enough. Second, some influence factors such as age, gender, a clinical

Table 1: Voxel values of the reduced glucose metabolism cerebral regions in three lung cancer groups

Cerebral areas	Adenocarcinoma	Squamous cell carcinoma	Small-cell carcinoma
Left superior middle and inferior temporal gyrus	397	312	1029
Right superior middle and superior temporal gyrus, right inferior parietal gyrus	435	497	1153
Left middle and superior frontal gyrus	383	501	846
Right hippocampus			227
Total regions	1217	1292	3255
t	14.33*	0.764†	10.07‡
P	<0.01*	0.525†	<0.01‡

*Adenocarcinoma versus small-cell carcinoma; †Squamous cell carcinoma versus adenocarcinoma; ‡Squamous cell carcinoma versus small-cell carcinoma.

stage, the mental factor have not been controlled strictly. These factors may have possibly affected the accuracy and preciseness of the results. Third, we did not evaluate the relationship between the resting brain glucose metabolic changes and patients' behavioristics. In future, stricter grouping studies and some prospective studies, such as the study combining brain PET and neuropsychiatric inventory or concerned hormone level should be conducted.

In conclusion, the brain metabolism in patients with lung cancer was characterized by regional cerebral resting glucose metabolic reduction. The brain hypo-metabolic changes were related to the histological types of lung cancer. The brain PET could be used to evaluate the mental status of patients with lung cancer, and hopefully provide a reliable imaging indicator for diagnosis and treatment of lung cancer patients with depression or affective disorders.

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