

学位論文の要旨

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学位論文名 The Effects of Aging on Changes in Regional Cerebral Blood Flow in Schizophrenia

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論文内容の要旨

INTRODUCTION

Although schizophrenia has increasingly been conceptualized as a neurodevelopmental disorder, there is mounting evidence on progression not only of cognitive but also of brain structural and functional pathology. Even though this progression might not be related to classical neuropathological markers of neurodegeneration such as astrogliosis, it has significant relevance for our understanding of the disease course, especially with respect to cognitive deterioration and general clinical outcomes. Alterations in brain structure have been observed in patients with schizophrenia at different stages of the disorder, including prodromal, first-episode, and chronic stages, and recent meta-analysis comparing the differences in the cross-sectional patterns of patients with healthy subjects suggest that there might be an increase in structural pathology over the course of the disease. In addition, both structural and functional imaging studies suggest changes at later disease stages that are suggestive of accelerated ageing compared with healthy individuals.

Thus, the present cross-sectional imaging studies of schizophrenia patients as well as the longitudinal MRI studies with follow-up periods of up to 10 years are suggestive of progressive changes exceeding those seen in healthy subjects. These changes seem to occur at different stages of the disease, including the transition to psychosis, the early course of schizophrenia, and senescence process.

In this study, we focused on cerebral blood flow and compared age-related changes in patients with schizophrenia with those in healthy controls

MATERIALS AND METHODS

Subjects

Schizophrenia patients (n = 44) were diagnosed according to DSM-IV criteria. Subjects were outpatients or inpatients of the Department of Psychiatry, Shimane University School of Medicine Hospital without acute psychiatric symptoms. Psychiatric symptoms were rated on the same day as the SPECT examination by a senior psychiatrist who was unaware of the SPECT findings and diagnosis using the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS). Diagnoses were determined by the consensus of three senior psychiatrists based on extended interviews and reviews of the Structured Clinical Interviews for DSM-IV (SCID) in the medical chart. In the patients, alcohol and substance abuse or dependence (other than nicotine) or the presence of a severe organic condition was eliminated from this study.

SPECT analysis procedure

Brain SPECT with 99-Tc-ethyl cysteinate dimer (Tc-99mECD) was performed during bed rest with no stimulation. SPECT images were acquired using a double-headed rotating gamma camera equipped with a fan-beam collimator. Two-sample t-test by SPM8 was used to determine which areas were affected by the decreasing rCBF between age and schizophrenia or control, between schizophrenia and control with age as covariates. In bilateral temporal lobes, we calculated a coefficient of determination (R² value) with rCBF data (ml/100g/min) and age. Moreover, step-wise multiple regression analysis was used to determine which areas were affected by the decreasing rCBF in schizophrenia as dependent variable, age, total time of treatment and overall neuroleptics dose as independent variables.

RESULTS AND DISCUSSION

The bilateral inferior frontal gyrus, left anterior cingulate of the patients with schizophrenia were decreasing brain perfusion related to age. The right cingulate gyrus, inferior parietal lobes, sublobar extranuclear and left postcentral gyrus in control subjects were decreasing brain perfusion related to age. The area of hypoperfusion related to age in schizophrenia patients and control was significantly different. In comparison to controls, the right insular, left superior temporal gyrus, anterior cingulate, thalamus, and lingual gyrus of the patients with schizophrenia were decreasing brain perfusion related to age.

An approximate curve showed that the subject's age was correlated with rCBF change in the bilateral temporal lobes, of control subjects and patients with schizophrenia, but that the

correlation between age (x) and rCBF (y) in patients with schizophrenia was more significant (left: $y = -0.3536x + 14.95$ $R^2 = 0.575$, $P < 0.001$; right: $y = -0.5179x + 21.895$ $R^2 = 0.7217$, $P < 0.001$) than control subjects (left: $y = -0.0935x + 3.3647$ $R^2 = 0.0423$, $P = 0.222$; right: $y = -0.1844x + 6.6327$ $R^2 = 0.1043$, $P = 0.051$) in neighboring areas where significant differences in the effects of age on perfusion were found in the patients with schizophrenia. Moreover, in comparison to controls, the brain perfusion related to age, total time of treatment and neuroleptic dose decreased in the right thalamus, occipital lobe and bilateral parietal lobes, frontal gyrus, cingulated gyrus of the patients with schizophrenia.

Several studies using SPECT have shown decreases in perfusion in several cortical and subcortical areas with age, while the characteristic frontotemporal pattern of perfusion decreases has been reported. Our findings have shown significantly correlation between the aging and the disease course effect of schizophrenia and a reduction in temporal perfusion and might be in accordance with a report that the rCBF reductions in the frontal lobe tended to extend to posterior brain regions in the chronic stage in schizophrenia. Although rCBF reduction might relate to not only aging but the disease duration and/ or its severity, progression of functional brain changes has rarely been assessed by longitudinal studies. Thus, our age-related design took advantage of imaging techniques to discover changes occurring over most of the adult life span. There are several confounding factors in our study. This study has a methodological limitation in the choice of patients, subtype, sex, and medication. But the patients are fairly young with a relatively brief duration of illness of 5 years and treatment was initiated in these patients very rapidly. So results of this study might reflect, particularly, the change of structure and function in middle-age patients with schizophrenia.

CONCLUSION

In this study, the patients with schizophrenia appeared to have significant bilateral temporal hypoperfusion related to age compared with control. And bilateral temporal rCBF is decreased in patients with schizophrenia and even more in older schizophrenia patients. These changes might be consistent with degenerative changes observed in the patients with schizophrenia and be a promising method for the efficient development of a treatment strategy by measuring temporal perfusion in patients with schizophrenia.