

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.

論文審査及び最終試験又は学力の確認の結果の要旨

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| <p>統合失調症は思春期・青年初期に好発し、慢性経過をたどる疾患である。これまでに形態的な脳画像研究においては、MRI(magnetic resonance imaging)を用いた比較で、統合失調症患者は健常者よりも加齢による脳容積の低下が強いことが示唆されている。一方、機能的な脳画像研究では SPECT(single photon emission computed tomography)を用いた脳血流画像において統合失調症患者では前頭葉を中心とした血流低下が示唆されている。しかし、統合失調症患者の脳血流と年齢との関係についての研究結果は報告されていない。</p> <p>そこで申請者は、統合失調症の脳血流における年齢の影響について検討した。具体的には統合失調症患者 44 名と健常者 37 名に脳血流 SPECT 検査を施行し、Patlak plot 法と呼ばれる非侵襲的方法を用いて各人の脳血流定量値を算出した後、SPM(statistical parametric mapping)による統計解析処理を行い、全脳を対象に統合失調症群と年齢を補正した健常群における脳血流について比較検討した。その結果、健常群に比べ、統合失調症群は両側側頭葉で統計学的に有意な血流低下を認めた。さらにその血流低下領域において、統合失調症群では年齢と共に脳血流低下がより顕著になることを明らかにした。これらの結果は統合失調症の治療期間や抗精神病薬投与量に影響を受けなかった。</p> <p>以上より、本研究は統合失調症において側頭葉の脳血流が低下することおよび、その低下が加齢とも関連することを明らかにした研究であり、この研究成果は統合失調症の病態把握や発症予防に寄与することが考えられるため、学位授与に値すると判断した。</p> | | | |
| 最終試験又は学力の確認の結果の要旨 | | | |
| <p>申請者は脳血流 SPECT 検査により、統合失調症患者において両側側頭葉血流が低下していること、同部の血流は年齢と負の相関があることを示した。これは統合失調症の診療に寄与する新たな知見である。周辺知識も豊富であり、学位授与に値すると判断した。(主査：北垣 一)</p> <p>申請者は統合失調症における脳血流量を多数の症例で検討し、両側側頭葉の血流低下を認め、さらに加齢性の低下が正常に比しより強いことを見出した。この結果は統合失調症の発症機序に示唆を与える知見であり、豊富な関連知識も有しており学位授与に値すると判断した。(副査：山口修平)</p> <p>申請者は、統合失調症患者に対する脳血流 SPECT の統計画像解析によって、統合失調症患者の上側頭回領域の有意な脳血流低下と加齢による同部の脳血流低下進行を見いだした。本研究の成果は本疾患の病態解明や新しい診断法につながりうるものであり、学位授与に値すると判断した。(副査：秋山恭彦)</p> | | | |

(備考) 要旨は、それぞれ400字程度とする。