学 位 論 文 の 要 旨

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学　位　論　文　名　Association of Vascular Risk Factors with Hippocampal Atrophy and Cognitive Impairment

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論 文 内 容 の 要 旨

INTRODUCTION

It is reported that aging and lifestyle-related disease are independently associated with increased risk of cognitive impairment. Vascular risk factors play an important role on brain structural change and cognitive impairment. However, it remains unclear whether risk factors increase the risk of cognitive decline through ischemic vascular changes or degenerative neuropathology.

A prospective study has shown that elderly diabetic patients were at greater risk for developing dementia than non-diabetic subjects. We have reported that patients with type 2 diabetes showed reduced volume of the hippocampus and the degree of atrophy was associated with decreased score of general cognitive function test.

Hypertension has been also reported to be a risk of dementia. Thus, both type 2 diabetes and hypertension could cause brain damage through large or small vasculopathy or/and neurodegenerative process.

This study aimed to clarify whether vascular risk factors including type 2 diabetes and hypertension affect brain structural changes and cognitive impairment, and whether asymptomatic ischemic lesions also contribute to cognitive impairment.

MATERIALS AND METHODS

Seven-hundred and eighty-four elderly volunteers participated in a medical examination of the brain at the Health Science Center in Shimane. The inclusion criteria were as follows: no history of neurological or psychiatric disorders including stroke and dementia, no abnormalities on neurological examination, and the provision of informed consent to participate in this study. The participants underwent medical check, laboratory test, neuropsychological test, and magnetic

resonance imaging (MRI). Clinical information included age, sex, histories of type 2 diabetes, hypertension, dyslipidemia, smoking, and regular alcohol consumption.

All participants were assessed using a neuropsychological test battery that included the Mini-mental state examination (MMSE) for general cognitive function, the Frontal assessment battery (FAB) for frontal lobe function, the Kohs' block test for visuospatial function, the Self-rating depression scale (SDS), and the Apathy scale (AS).

MRI examinations were performed, using a 1.5-Tesla MRI. The volume of hippocampus was quantified with an SPM2-based VBM analysis procedure. The software for the measurement is distributed under the name as voxel-based specific regional analysis system for Alzheimer's disease (VSRAD). VSRAD automatically calculated Z value, which reflects the severity of gray matter loss in the hippocampal region of an individual subject by comparing it with the original normal database template. We defined hippocampal atrophy ranged from grade 1 to 3; grade 1 for Z value between 0.0 and 1.0, grade 2 for Z value between 1.0 and 2.0, grade 3 for Z value more than 2.0. In a clinical setting, grade 1 means no atrophy, grade 2 is interpreted as slight atrophy, grade 3 is indicative of significant atrophy.

We also evaluated silent brain infarction (SBI), periventricular hyperintensity (PVH), deep or subcortical white matter hyperintensity (DSWMH) as asymptomatic ischemic brain lesions.

A general linear model was used for the analysis of influence of vascular risk factors and MRI changes on cognitive impairment and relationship between vascular risk factors and MRI changes with adjustment of age and sex.

A level of $p < .05$ was accepted as statistically significant. Statistical analysis was performed with the SPSS software package (version 22, IBM Co.).

The study design was approved by the institutional Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

RESULTS AND DISCUSSION

Type 2 diabetes was significantly associated with lower scores on FAB and Kohs' block test, but MMSE, SDS and AS scores were not affected by type 2 diabetes. On the other hand, hypertension and dyslipidemia did not affect any neuropsychological test scores. We found that type 2 diabetes and hypertension had significant contributions to hippocampal atrophy. Furthermore, we studied the relationship between asymptomatic ischemic brain lesions including SBI, PVH, and DSWMH and vascular risk factors. Hypertension had significant influences on asymptomatic ischemic brain lesions. This indicates that hypertension affects both hippocampal atrophy and asymptomatic ischemic lesions, whereas type 2 diabetes contributes exclusively to hippocampal atrophy.

Hippocampal atrophy was significantly related to low scores on FAB and Kohs' block test,

but not to MMSE score. Among asymptomatic ischemic brain lesions, SBI affected negatively to MMSE score and Kohs' block test score, and DSWMH was associated with stronger depressive state. Apathy score was not related to any brain structural changes.

Type 2 diabetes was associated with atrophic changes in the hippocampus, but not ischemic vascular changes, whereas hypertension was associated with both atrophic changes and ischemic vascular changes. In addition, the frontal lobe and visuospatial dysfunction associated with type 2 diabetes were correlated with hippocampal degenerative pathology. Thus, this study supports the notion that hippocampal degenerative change rather than ischemic vascular changes might be the main pathology underlying cognitive impairment, independent of aging, in type 2 diabetic subjects.

Our study suggests that type 2 diabetes might promote atrophy of the hippocampus. MRI studies investigating the impact of type 2 diabetes on brain structures have been conducted on people without dementia. These studies demonstrated decreases in brain volume affecting both the white and grey matters in individuals with type 2 diabetes. Although our volumetric measurement did not cover brain areas other than the hippocampus, the medial temporal lobe seems particularly vulnerable to diabetes-related brain atrophy.

The present study demonstrated that hypertension in addition to type 2 diabetes also contributed to the reduction of the hippocampal volume independently, although this effect was not as strong as that of type 2 diabetes.

Our study suggests that ischemic vascular changes are not associated with diabetes-related cognitive impairments and that degenerative changes are a predominant pathway linking diabetes and cognition. Thus, degenerative pathology rather than cerebrovascular lesions might play a key role in diabetes-related cognitive impairments, specifically frontal executive dysfunction.

Recent brain network analyses have revealed that the medial temporal lobe is one of the core regions involved in the default mode network. This network also included the precuneus, posterior cingulate gyrus, and medial frontal lobe. Thus, the hippocampal degenerative change associated with type 2 diabetes could contribute frontal executive dysfunction.

The major limitation of this study was its cross-sectional design, which made it difficult to determine the causative relationship between type 2 diabetes, hippocampal atrophy, and cognitive impairments. Longitudinal studies including brain imaging and neuropsychological assessment are needed to understand the mechanisms of the link between type 2 diabetes and cognitive impairments.

CONCLUSIONS

Our study demonstrated that patients with type 2 diabetes showed reduction in frontal executive and visuospatial functions and this association was correlated with neurodegenerative processes. Our study suggested that pharmacological intervention and life-style approaches might

effectively prevent neurodegenerative processes and dementia in individuals with type 2 diabetes.

This study also indicates the importance of monitoring brain morphological changes in the routine follow-up of type 2 diabetic patients, because both type 2 diabetes and AD are highly prevalent among the elderly.

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論文審査の結果の要旨

認知機能障害のリスク増大に、生活習慣病の関与が報告されている。高血圧症は血管構造の破綻から脳血流、認知機能を低下させ、糖尿病も認知機能障害のリスクと考えられている。しかし、動脈硬化危険因子が、いかに脳の構造的変化や無症候性血管病変を惹起し認知機能に影響するかは明らかでない。申請者はヘルスサイエンスセンター島根の健診を受診した神経疾患の既往のない784名について、高血圧、2型糖尿病、脂質異常症の危険因子と各種神経心理学的検査結果、および頭部MRI画像との関連を横断的に統計解析で評価した。頭部MRIは、海馬萎縮、白質障害、無症候性虚血性病変の程度を数値化した。その結果、2型糖尿病および高血圧症は、独立して海馬萎縮と関連した。2型糖尿病は、遂行機能、空間認知機能低下と有意に関連したが、高血圧症や脂質異常症では関連がみられなかった。高血圧症では、脳の白質病変や無症候性虚血性病変に関連した海馬萎縮が示唆されたが、2型糖尿病は直接海馬萎縮を惹起して認知機能低下を生じたことが示唆された。また、脳の構造変化と認知機能の解析から、海馬萎縮は遂行機能、空間認知機能低下と有意に関連した。本研究は2型糖尿病が海馬萎縮に直接関与し、特定の認知機能に影響を及ぼすことを大規模横断研究で証明した先端的成果である。2型糖尿病や高血圧症に伴う認知機能障害の予防や治療に示唆を与える臨床的重要性をもつ研究であり、学位授与に値する。