学 位 論 文 の 要 旨

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学　位　論　文　名　Association of Mild Kidney Dysfunction With Silent Brain Lesions in Neurologically Normal Subjects

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論 文 内 容 の 要 旨

INTRODUCTION

Recently, the relation between chronic kidney disease (CKD) and cerebrovascular disease has been highlighted in not only symptomatic but also asymptomatic cases. Several population studies have reported that there is an independent association of estimated glomerular filtration rate (eGFR) with silent brain infarction (SBI), white matter lesions, and microbleeds (MBs), which are important independent factors for poor prognosis of patients with CKD. Although a large number of studies reported the relationship between each silent brain lesion and CKD, there are few reports in which comprehensive analyses were performed for the association of CKD with all types of subclinical brain lesions. Thus, the aim of this study was to investigate the relationship between all silent brain lesions and CKD, and provide new insights regarding the relative significance of CKD to each brain lesion in a large-scale, cross-sectional, neurologically normal population.

MATERIALS AND METHODS

We studied a total of 1,937 subjects (1,012 men and 925 women) with a mean age of 59.4 ± 7.9 years (range: 27 to 86 years). The screening system included collection of medical, neurological, and psychiatric history, formal neurological examinations by an experienced neurologist, neuropsychological assessment, MRI of the head, and blood and urine analyses. The inclusion criteria for this study were the following: no history of neurological or psychiatric disorders, no abnormalities on neurological examination, no severe medical illness, and written

informed consent to participate in this study. The study design was approved by the institutional ethics committee of Shimane University Hospital.

Venous blood samples were collected from all subjects after an overnight fast, and the sera were used for measurements of fasting blood glucose, HbA1c, lipid, and creatinine using an autoanalyzer. The level of urinary protein was examined and we defined positive proteinuria when the dipstick scale showed a value ≥1+. Kidney function was estimated by the calculated creatinine clearance using the 4-variable Modification of Diet in Renal Disease equation. CKD was defined as either positive proteinuria or eGFR <60. Subjects with an eGFR <30 were not included in the present study.

MRI scans of the brain were performed using a 1.5-Tesla MRI system (Symphony Ultra Gradient, Siemens). SBI was defined as a focally hyperintensity lesion >3 mm in diameter in the T2WI, corresponding to a hypointensity lesion in the T1WI. PVH was graded using a scale of 0 to 4, and we defined grade 3 and 4 as PVH +. SWML was graded using a scale of 0 to 3 according to the Fazekas' grading scale, and we defined grades 2, 3, and 4 as SWML +. MBs were defined as homogenous round foci of signal loss that were 2–10-mm in diameter in T2*WI.

Baseline characteristics were compared between the CKD and non-CKD group using the student's *t*-test for parametric data and the Mann-Whitney U-test for non-parametric data. The relationship between MRI changes and CKD was analyzed using the Pearson's chi-squired test. P values adjusted for age and sex were also given for univariate analysis. After adjustment for age and sex, the multivariate logistic models were adopted to estimate the risks of the presence of CKD for silent brain lesions.

RESULTS AND DISCUSSION

Of 1,937 subjects, the prevalence of CKD was 8.7%. The mean age of CKD subjects was significantly higher than the non-CKD subjects. After adjusted for age and sex, CKD was associated with hypertension and dyslipidemia. All silent lesions on MRI, including SBI, subcortical white matter lesion (SWML), periventricular hyperintensity (PVH), and MBs were more prevalent in subjects with CKD after adjusted for age and sex. Age had a strong effect on all brain lesions. After adjustment for age and sex, hypertension was associated with the presence of all brain lesions except for PVH, and diabetes mellitus also affected the presence of SBI and MBs, whereas dyslipidemia was not related to any silent brain lesions.

With binary logistic regression analysis, the presence of CKD was a significant risk factor for all types of silent brain lesions independent of other risk factors. The odd's ratio was the highest for MBs among the silent brain lesions. Although hypertension was the strongest risk factor for SBI, other brain lesions were affected more strongly by the presence of CKD compared to hypertension.

The current study demonstrated the independent and significant role of CKD on silent brain lesions in addition to traditional vascular risk factors. To our best knowledge, this is the largest

cross-sectional study that examined the relationship of CKD to structural brain changes in a general healthy population. Not only univariate analysis but also multivariate logistic regression analysis showed aggravating influence of CKD on any silent brain lesions independent of other confounding vascular risk factors.

The current study demonstrated that even mild CKD is associated with SBI independently of hypertension and age. Among all silent brain lesions only SBI was affected more strongly by hypertension than CKD (odd's ratio: 2.31 vs 1.90), and this pattern was also reported in a recent study. The relatively strong contribution of hypertension to SBI indicates that blood pressure control may be critically important to prevent SBI in subjects with mild CKD.

Although hypertension is the strongest risk factor for SBI, other MRI lesions, including PVH, SWML, and MBs, are more strongly influenced by the presence of CKD than hypertension in the current study. There were some differences in the relationship between CKD and SWML or PVH. PVH was affected only by age and CKD, whereas SWML was affected by hypertension in addition to age and CKD. This differential association might be attributable to the histopathological features of PVH, which involve the disruption of the ependymal lining with the sub-ependymal widening of the extracellular space.

MBs are considered clinically silent but are strongly associated with advanced small vessel or microvascular disease. Previous reports have examined the relationship between MBs and CKD in specific populations such as patients with intracranial hemorrhage, those with hypertension, or those with severe kidney dysfunction. The current study demonstrated that even mild kidney dysfunction could be a risk factor for the appearance of MBs independent of hypertension in a general population. Furthermore, MBs was affected by CKD most strongly among silent brain lesions. Since MBs are a strong risk factor for future cerebral hemorrhage and ischemic stroke, active interventions that prevent kidney dysfunction may be important for reducing occurrence of future stroke in subjects with risk factors for CKD.

CONCLUSION

The current study demonstrated that even mild CKD is associated with all types of silent brain lesions independent of age, sex, hypertension, and diabetes mellitus in neurologically normal population. Specifically MBs was most strongly associated with the presence of CKD. Further prospective studies are required to define the causal relationship between silent brain lesions and CKD.