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Original Paper

Association of Mild Kidney Dysfunction with Silent Brain Lesions in Neurologically Normal Subjects

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Key Words
Chronic kidney disease · Silent brain lesions · Risk factors · Small vessel disease

Abstract
Background: Chronic kidney disease (CKD) has been closely associated with stroke. Although a large number of studies reported the relationship between CKD and different types of asymptomatic brain lesions, few comprehensive analyses have been performed for all types of silent brain lesions. ***Methods:*** We performed a cross-sectional study involving 1,937 neurologically normal subjects (mean age 59.4 years). Mild CKD was defined as an estimated glomerular filtration rate between 30 and 60 ml/min/1.73 m^2 or positive proteinuria. ***Results:*** The prevalence of mild CKD was 8.7%. Univariate analysis revealed an association between CKD and all silent brain lesions, including silent brain infarction, periventricular hyperintensity, subcortical white matter lesion, and microbleeds, in addition to hypertension and diabetes mellitus after adjusting for age and sex. In 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. ***Conclusions:*** These results suggest that mild CKD is independently associated with all types of silent brain lesions, even in neurologically normal subjects.

Introduction

Recently, the relation between chronic kidney disease (CKD) and cerebrovascular disease has been highlighted not only in symptomatic but also in asymptomatic cases [1–6]. 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 a poor prognosis of patients

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with CKD [7–14]. 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

Study Population

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 27–86). All subjects voluntarily participated in the brain checkup system at the Shimane Health Science Center between January 2001 and December 2008. 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 following inclusion criteria for this study were applied: 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.

Acquisition of Laboratory Data

Venous blood samples were collected from all subjects after an overnight fast, and the sera were used for the measurements of fasting blood glucose, HbA_{1c}, lipid, and creatinine using an autoanalyzer. The level of urinary protein was examined using a urine dipstick and classified into 4 levels: negative (dipstick reading −), trace (±), mild (1+), and severe (≥2+). The amount of urine protein estimated by the dipstick reading was as follows: trace (15–29 mg/dl), mild (30–99 mg/dl), and severe (≥100 mg/dl). We defined positive proteinuria when the dipstick scale showed a value of ≥1+. Kidney function was estimated by the calculated creatinine clearance using the 4-variable Modification of Diet in Renal Disease equation as follows: eGFR (ml/min/1.73 m^2) = 194 × $Cr^{-1.094}$ × $age^{-0.287}$ for men, and 194 × $Cr^{-1.094}$ × $age^{-0.287}$ × 0.739 for women. CKD was defined as either positive proteinuria or eGFR <60 ml/min/1.73 m^2. Subjects with an eGFR <30 ml/min/1.73 m^2 were not included in the present study. We described the methods for the assessment of other laboratory and demographic data and MRI findings in the online supplementary section (www.karger.com/doi/10.1159/000373916).

Statistical Analysis

Baseline characteristics were compared between the CKD and non-CKD groups using the Student t test for parametric data and the Mann-Whitney U test for nonparametric data. The relationship between MRI changes and CKD was analyzed using the Pearson χ^2 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 [odds ratio (OR) and 95% confidence interval] of the presence of CKD for silent brain lesions.

Results

The clinical and demographic details of the subjects are presented in table 1. Among the 1,937 subjects, the prevalence of CKD was 8.7%. The mean age of CKD subjects was significantly higher than that of the non-CKD subjects. Male subjects were more frequent in the CKD

Table 1. Subject background

	CKD	Non-CKD	p value	p value adjusted for age and sex
Number of subjects	168	1,769		
Age, years	063.7	0,059.0	<0.0001	
Sex (male/female), %	059.8/40.2	0,051.5/48.5	<0.05	
Smoking habit, %	018.3	0,017.2	n.s.	
Alcohol habit, %	039.1	0,036.3	n.s.	
Education, years	012.1	0,012.5	n.s.	
Hypertension, %	075.7	0,064.0	<0.002	<0.02
Diabetes mellitus, %	013.6	0,0 8.8	<0.04	n.s.
Dyslipidemia, %	032.5	0,024.2	<0.02	<0.005

n.s. = Not significant.

Table 2. Prevalence of silent brain lesions in the CKD and non-CKD groups

	CKD	Non-CKD	p value	p value adjusted for age and sex
SBI, %	15.4	6.7	<0.0001	<0.02
SWML scale ≥2, %	22.6	10.9	<0.0001	<0.02
PVH scale ≥3, %	11.3	3.4	<0.0001	<0.02
MBs, %	6.0	1.4	<0.0001	<0.002

group. After adjusting for age and sex, CKD was associated with hypertension and dyslipidemia. Smoking and alcohol habit did not affect the occurrence of CKD.

Table 2 compares the prevalence of silent brain lesions between CKD and non-CKD subjects. 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 adjusting for age and sex. It is plausible that the presence of silent brain lesions is also related to hypertension, diabetes mellitus, and dyslipidemia in addition to age and sex. Then, we analyzed the effects of these demographic and clinical data on the brain lesions (table 3). Age had a strong effect on all brain lesions. Male sex was significantly associated with the presence of SBI only. 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 lesion.

On the basis of the above findings, we analyzed the risk of CKD on silent brain lesions using binary logistic regression analysis to exclude the influence of confounding risk factors (table 4). The presence of CKD was a significant risk factor for all types of silent brain lesions, independent of other risk factors. The OR 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.

Discussion

A meta-analysis of the influence of CKD on stroke risk documented that low eGFR is independently related to the incidence of stroke across a variety of participants and studies [15]. The current study demonstrated the independent and significant role of CKD on silent brain

Table 3. Demographic and clinical data in subjects with and without silent brain lesions

	SBI–	SBI+	p value	PVH–	PVH+	p value	SWML–	SWML+	p value	MBs–	MBs+	p value
Number of subjects	1,794	144		1,859	79		1,706	232		1,904	34	
Age, years	59.1	63.9	<0.0001	59.1	67.4	<0.0001	58.8	64.2	<0.0001	59.3	64.1	<0.0001
Sex (male), %	51.6	60.4	<0.05	52.2	54.4	n.s.	52.8	48.1	n.s.	52.1	58.8	n.s.
Smoking habit, %	17.2	18.1	n.s.	17.3	16.5	n.s.	17.5	16.0	n.s.	17.2	23.5	n.s.
Alcohol habit, %	36.4	38.9	n.s.	36.4	40.5	n.s.	36.8	35.5	n.s.	36.5	41.2	n.s.
Education, years	12.5	11.6	n.s.	12.4	11.9	n.s.	12.5	11.8	n.s.	12.4	11.7	n.s.
Hypertension, %	63.7	81.3	<0.0001 (<0.0001)	64.5	77.2	<0.05 (n.s.)	63.9	73.6	<0.005 (<0.02)	64.7	85.3	<0.02 (<0.05)
Diabetes mellitus, %	8.6	17.4	<0.0001 (<0.05)	8.9	16.5	<0.05 (n.s.)	9.1	10.0	n.s. (n.s.)	9.0	23.5	<0.005 (<0.05)
Dyslipidemia, %	24.9	25.7	n.s.	25.2	19.0	n.s.	24.6	27.7	n.s.	24.9	29.4	n.s.

p values in parentheses are adjusted for age and sex. n.s. = Not significant.

Table 4. Binary logistic regression analysis of risk factors for silent brain lesions

	SBI		PVH		SWML		MBs	
	OR	p value	OR	p value	OR	p value	OR	p value
Age ≥65 years	2.26 (1.59–3.22)	<0.0001	5.99 (3.59–9.99)	<0.0001	3.06 (2.30–4.07)	<0.0001	2.27 (1.12–4.5)	<0.05
Male sex	1.40 (0.98–2.00)	0.066	1.14 (0.71–1.83)	n.s.	0.86 (0.64–1.14)	n.s.	1.17 (0.58–2.38)	n.s.
Hypertension, yes	2.31 (1.50–3.57)	<0.0001	1.71 (0.99–2.96)	n.s.	1.49 (1.08–2.04)	<0.02	2.73 (1.04–7.14)	<0.05
Diabetes mellitus, yes	1.85 (1.14–2.98)	<0.02	1.61 (0.84–3.07)	n.s.	0.95 (0.59–1.53)	n.s.	2.50 (1.09–5.75)	<0.05
CKD, yes	1.90 (1.18–3.05)	<0.01	2.44 (1.38–4.32)	<0.002	1.89 (1.26–2.84)	<0.005	3.30 (1.51–7.20)	<0.005

Figures in parentheses are 95% confidence intervals.

lesions in addition to traditional vascular risk factors. To the best of our knowledge, this is the largest cross-sectional study that examined the relationship of CKD with structural brain changes in a general, healthy population. Although a large number of studies have revealed that each silent brain lesion is associated with CKD, there are few comprehensive reports that include all asymptomatic brain lesions. Not only univariate analysis but also multivariate logistic regression analysis showed an 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. This is in line with recent studies reporting that CKD is one of the potential risk factors for SBI, independent of hypertension [3, 7–9, 16]. Among all silent brain lesions, only SBI was affected more strongly by hypertension than CKD (OR 2.31 vs. 1.90), and this pattern was also reported in a recent study [7]. 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 subependymal widening of the extracellular space [17]. With the progression of CKD, the kidneys lose their ability to effectively remove toxic compounds from the bloodstream for the subsequent formation of urine, resulting in their accumulation in the body. It seems that the

accumulation of these uremic toxins leads to nontraditional risk factors such as inflammation, endothelial dysfunction, sympathetic overactivation, protein-energy wasting, oxidative stress, vascular calcification, and volume overload [18]. Consequently, CKD may impair endothelial dysfunction, resulting in distributed damage of brain white matter.

MBs are considered clinically silent but are strongly associated with advanced small vessel or microvascular disease [19]. The pathological significance of MBs depends on their location in the brain; recent evidence indicates that lobar and deep-brain MBs are associated with cerebral amyloid angiopathy and hypertensive vasculopathy, respectively [20]. 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 [12–14]. 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 were most strongly affected by CKD among silent brain lesions. As suggested for SBI and SWML, microvascular pathologic processes mediated by inflammatory and oxidative processes could be responsible for the association between MBs and CKD. Since MBs are a strong risk factor for future cerebral hemorrhage and ischemic stroke [21], active interventions that prevent kidney dysfunction may be important for reducing the occurrence of a future stroke in subjects with risk factors for CKD.

Our study has several limitations. First, this was a cross-sectional study. A longitudinal study may be warranted to confirm the causal relationship between CKD and silent brain lesions. A prospective study could also address the important question of whether the preservation of kidney function prevents the deterioration of silent brain lesions and eventually reduces the occurrence of stroke. Another limitation of the study is that our subject selection might have been biased, because all subjects were recruited from a group of individuals who voluntarily participated in the brain checkup system. These individuals may have had different demographic characteristics (e.g., motivation to seek healthcare and economic level) than subjects included in other population-based cohort studies. However, this checkup system has provided us with an opportunity to study the relationship between kidney function and detailed MRI findings in a large number of neurologically normal subjects.

In 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 a neurologically normal population. Specifically MBs were most strongly associated with the presence of CKD. Further prospective studies are required to define the causal relationship between silent brain lesions and CKD.

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