Original Paper

Cognitive Impairment and Structural Neuroimaging Abnormalities Among Patients with Chronic Kidney Disease

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Key Words

Peritoneal dialysis • Hemodialysis • Chronic kidney disease • Cognitive impairment • Brain magnetic resonance imaging

Abstract

Background/Aims: Cognitive impairment and abnormal structural neuroimaging is common in chronic kidney disease patients. We aimed to explore its association with dialysis modality and the relationship between cognitive impairment and abnormal structural neuroimaging.

Methods: Sixty peritoneal dialysis patients and 30 hemodialysis and 30 non-dialyzed stage 3-5 chronic kidney disease patients without history of stroke were enrolled for the study. Participants were matched for age, gender, education, diabetes status, and dialysis duration (if appropriate). Cognitive functions were measured using a battery of recognized instruments. Brain features were examined with 3-dimensional magnetic resonance imaging. **Results:** Cognitive impairment was significantly more severe in dialysis patients than in non-dialyzed patients. The global and specific cognitive function were not significantly different between patients on peritoneal dialysis and hemodialysis. Hemodialysis patients had more severe white matter hyperintensity, sulcal and ventricular atrophy, and SVIs than other patients. In all groups, higher white matter grade, ventricular grade, and hippocampal atrophy were significantly associated with global cognitive impairment, with hazard ratios of 1.80 (1.22-2.64), 1.67 (1.09-2.57), and 2.49 (1.07-5.77), respectively. White matter grade was also significantly associated with delayed memory (hazard ratio 1.63; 1.12-2.39). **Conclusion:** Dialysis modality showed no association with cognitive impairment, although hemodialysis patients had more

severe neuroimaging abnormalities. For the whole group, white matter hyperintensity, and ventricular and hippocampal atrophy, were independently associated with global cognitive impairment in chronic kidney disease patients.

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Published by S. Karger AG, Basel

Introduction

Cognitive impairment (CI), a common phenomenon in chronic kidney disease (CKD), is seen in 27%-67% of patients with end-stage renal disease including peritoneal dialysis (PD) and hemodialysis (HD) [1-4], and is closely associated with mortality and technical survival in dialysis patients [1]. Also, magnetic resonance imaging (MRI) of the brain showed that structural neuroimaging abnormalities such as white matter hyperintensity (WMH), brain atrophy, and overt or silent cerebral infarction is prevalent among HD [5, 6] or PD patients [7, 8], as compared to healthy or CKD controls. However, a few studies have explored the influence of dialysis modality on the prevalence of CI [3, 9, 10], or on the prevalence of structural and functional neuroimaging abnormalities [11, 12].

The link between brain morphological changes and CI in the general population has been known for a long time [13-15]. Cardiovascular disease (CVD) has been suspected to mediate this association because they share common pathway such as hypertension, diabetes mellitus (DM), hyperlipidemia, anemia, malnutrition, inflammation, and oxidative stress [4, 16, 17]. Some reports have indicated a link between CI or dementia and abnormal morphological changes of brain or alterations in magnetic resonance spectroscopy among HD or non-dialyzed CKD patients [6, 18, 19]; however, these studies did not include PD patients. Accordingly, it is hard to draw a general concept on the potential link of CI and structural neuroimaging findings for the whole CKD group.

Therefore, we wished to explore the influence of dialysis modality on CI and morphological brain changes among CKD patients. We further aimed to identify the potential links between CI and morphological brain changes in CKD patients.

Materials and Methods

Study Design and Participants

This is an add-on study to the previous multi-center cross-sectional survey of cognitive function in PD patients conducted between March 2013 and March 2014 [20]. Among the 222 patients enrolled from Peking University First Hospital in that survey, 60 PD patients who satisfied the inclusion and exclusion criteria of this study and were willing to participate in the neuroimaging examination were recruited. The other study participants—30 HD patients and 30 non-dialyzed CKD patients—were recruited between March 2014 and March 2015. Patients were case-matched for age, gender, education, and DM; HD and PD patients were additionally matched for dialysis vintage. All PD patients were prescribed lactate-buffered glucose dialysate, delivered using a twin-bag connection system (Baxter Healthcare, Guangzhou, China) by the continuous ambulatory PD modality. HD patients receiving hemodialysis for 4 hours 2-4 times weekly, using polysulfone membrane hemodialyzer (FX60, FX80 and FX100, Fresenius Medical Care, Beijing, China) and glucose-containing and glucose-free dialysate (Baxter Healthcare, Guangzhou, China; Ziweishan Pharmaceutical Co. Ltd., Hebei, China). The study flowchart is shown in supplemental file.

Participants were included if they were ≥ 18 years of age, had clinically stable disease, had been undergoing dialysis ≥ 3 months (if appropriate), and had no history of known stroke. Patients were excluded if they had had a systemic infection, acute cardiovascular event, active hepatitis, cancer, surgery, or trauma in the month prior to the study. Severe visual handicap, language incompatibility, illiteracy, mental disease (preexisting dementia or confusion, or any mental disorder), upper limb disability, and ineligibility for MRI due to the presence of metallic or electronic implants were also grounds for exclusion from the study.

Clinical Characteristics

Patient characteristics and comorbidities were recorded; this included age, gender, educational level, dialysis duration, body mass index, systolic and diastolic blood pressure, primary kidney disease, and history of DM or CVD. Educational level was recorded as the highest school level at which a diploma was received, i.e., elementary school or lower, middle school, high school, or above high school. CVD was recorded if one of the following conditions was present: angina, New York Heart Association class III-IV congestive heart failure, transient ischemic attack, history of myocardial infarction or cerebrovascular accident, and peripheral arterial disease [21].

Laboratory Investigations

Venous blood was sampled after overnight fasting. Hemoglobin, serum creatinine, albumin, triglyceride, total cholesterol, calcium, phosphate, potassium, sodium, intact parathyroid hormone (iPTH), and high-sensitivity C-reactive protein (hs-CRP) values were calculated as the mean of measurements taken over the preceding 3 months. Biochemical profiles were investigated using an automated Hitachi chemistry analyser. Dialysis adequacy was defined as total Kt/V and creatinine clearance calculated from urea, creatinine from 24-hour urine, dialysate and blood sample.

Cognitive Function

The Modified Mini-Mental State Examination (3MS) [22] was used to test overall cognitive function. Global CI has been defined previously as a score of <80 in the 3MS test [23]. However, because mean scores on the 3MS vary by education, we used a 3MS cutoff point of <75 for individuals with less than high school education and a cutoff point of <80 for individuals with high school education [24].

Specific cognitive function was measured by executive function i.e. Trail-making Tests A (Trail A) and B (Trail B), immediate memory, delayed memory, visuospatial skill, and language ability using subtests of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The Trail A and Trail B [25] were used to test executive function, including decision-making and processing speed. Executive dysfunction was defined as a Trails A score >75 seconds and a Trails B score >180 seconds [26]. In addition, subtests of RBANS were adopted to assess immediate memory (list learning and story memory); delayed memory (list recall, list recognition, story recall, and figure recall); visuospatial skill (figure copy); and language ability (picture naming and semantic fluency) [27]. The reliability and validity of RBANS in the Shanghai and Beijing population has already been established [28]. The raw scores were transformed to age-standardized T scores for all subtests of RBANS. T scores less than 1 SD below the published mean in the corresponding education-grouped Chinese population were identified as impaired for each test. Assessments of cognitive function were performed in a separate room, with one medical staff to one patient. Totally, two medical staffs participated in this study after being trained in the methods and processes to ensure integrity and accuracy in assessment.

The timing of the cognitive tests was after dialysis treatments for hemodialysis patients, and was after clinical follow-up for peritoneal dialysis patients, during 8:00 to 12:00 and 13:00 to 17:00.

Magnetic Resonance Imaging (MRI)

Patients without history of stroke or contraindications for MRI were invited to undergo a 3-dimensional MRI (3D-MRI) scan as introduced by a previous literature [20]. MRI was performed with a 3.0-T MR imaging unit (Signa Excite; GE Medical Systems, Milwaukee, WI, USA) using an eight-channel head coil. For each patient, the following sequences were obtained: axial 3D T1-weighted fast spoiled gradient echo (echo time, 3.9 ms; flip angle, 20; field of view, 220 mm; section thickness, 1.3 mm); axial T2-weighted (repetition time, 5000 ms; echo time, 126 ms, field of view, 240 mm; section thickness, 6.0 mm); and axial T2 fluid-attenuated inversion recovery (FLAIR; repetition time, 8825 ms; TE, 100 ms; inversion time, 2400 ms; field of view, 240 mm; section thickness, 6.0 mm). White matter disease was defined as hyperintensity on FLAIR and T2-weighted images, with no corresponding T1 abnormality. Two neuroradiologists blinded to the clinical information from the study semi-quantitatively graded cerebral atrophy, hippocampal size, and WMH, using previously validated criteria [5]. To evaluate the inter-observer agreement level, the kappa coefficient was obtained. Kappa coefficient was categorised as: weak agreement ($\text{Kappa} \leq 0.4$), moderate agreement ($0.4 < \text{Kappa} \leq 0.75$); good agreement ($\text{Kappa} > 0.75$). Cerebral atrophy was assessed by sulcal prominence

and ventricular size. Sulcal prominence ranged from grade 0 (small sulci) to grade 9 (very large sulci) and ventricular size ranged from grade 0 (slit-like) to grade 9 (markedly enlarged); in both cases, higher grade indicated more severe atrophy. Hippocampal size was graded on a scale of 0 (no atrophy) to 3 (severe atrophy). Severity of WMH was scored on a scale of 0 (no detectable change) to 9 (all white matter involved). Large-vessel infarcts (LVI) were defined as infarcts >1.5 cm in a major vascular territory. Any infarct in a cortical location was considered a manifestation of large-vessel disease. A small-vessel infarct (SVI) was defined as a focal subcortical brain lesion between 3 mm and 1.5 cm in size that was hyperintense on T2-weighted images and hypointense on T1-weighted images.

Statistical Analysis

Continuous data were presented as means $\pm$ SD, except for dialysis duration, hs-CRP, and iPTH, which were presented as medians with interquartile ranges due to high skew. Categorical variables were presented as percentage or ratio. Demographic data, biochemistry profiles, cognitive function, and brain morphological changes were compared between PD, HD, and non-dialyzed CKD patients by using the *t* test for normally distributed continuous variables, the chi-square test for categorical variables, or the Mann-Whitney U test for skewed continuous variables.

To assess whether general and specific cognitive function were related to brain morphological changes and clinical characteristics, the Spearman correlation analysis was performed first. Then, we examined the relationship between brain morphological abnormalities and general and specific CI by using univariate logistic regression models. Recognized influence factors for CI including age, education, diabetes, CVD history, serum albumin, and sodium were further put into a multivariable logistic regression model to identify if brain morphological abnormalities were independently associated with general and specific CI.

All probabilities were two-tailed, and the level of significance was set at 0.05. Statistical analysis was performed using SPSS for Windows, software version 13.0 (SPSS Inc., Chicago, IL).

Results

Basic Characteristics

A total of 60 PD, 30 HD, and 30 non-dialyzed stage 3-5 CKD patients (2:1:1) were enrolled in this study. Participants were matched for age, gender, educational level, and DM status; PD and HD patients were additionally matched for dialysis duration. As shown in Table 1, there were no significant differences between the groups in gender distribution, mean age, body mass index, blood pressure, dialysis duration, educational status, or prevalence of DM and cardiovascular disease. Patients with non-dialyzed CKD had significantly better nutritional status, less inflammation, and more balanced mineral status. Patients on PD were more likely to have lower serum albumin, potassium, and iPTH levels, while having higher total cholesterol levels, than HD patients ($P < 0.05$). There were no significant differences in hemoglobin, serum creatinine, calcium, phosphate, sodium, and hs-CRP values between PD and HD patients ($P > 0.05$).

Cognitive Function and Structural Neuroimaging Findings

Global and specific cognitive functions were assessed on the basis of the scores achieved in the tests. As shown in Table 2, non-dialyzed CKD patients had significantly higher scores for global cognitive function as assessed by 3MS, shorter completion time on Trail A and Trail B, and higher scores for delayed memory and visuospatial ability than case-matched PD and HD patients ($P < 0.05$). Non-dialyzed CKD patients also had higher scores for immediate memory than PD patients ($P = 0.046$); they showed significantly lower prevalence of executive dysfunction and visuospatial ability impairment than PD and HD patients, and lower prevalence of delayed memory impairment than HD patients ($P < 0.05$). HD patients were not significantly different from case-matched PD patients in global and specific cognitive function ($P > 0.05$). There were no significant differences in scores for language ability and prevalence of language impairment between PD, HD, and non-dialyzed CKD patients ($P > 0.05$).

Table 1. Clinical characteristics of peritoneal dialysis, hemodialysis, and stage 3-5 chronic kidney disease patients

	PD (n = 60)	HD (n = 30)	CKD stage 3-5 (n = 30)	P ^{&}
Age (years)	57.7 ± 7.8	56.5 ± 11.8	53.4 ± 12.4	0.17
Dialysis duration (months)	43 (15-90.5)	48 (22.5-99)	NA	0.23
Male (%)	27 (45%)	19 (63.3%)	20 (66.7%)	0.09
Education level				0.43
Primary school or lower	6 (10%)	2 (6.7%)	0 (0%)	
Middle school	14 (23.3%)	7 (23.3%)	4 (13.3%)	
High school	24 (40%)	11 (36.7%)	13 (43.3%)	
College or higher	16 (26.7%)	10 (33.3%)	13 (43.3%)	
Diabetes (%)	27 (45%)	10 (33.3%)	8 (26.7%)	0.21
Cardiovascular disease (%)	27 (45%)	9 (30%)	6 (20%)	0.051
Body mass index (kg/m ²)	22.8 ± 3.6	23.5 ± 3.7	24.9 ± 4.4	0.07
Systolic blood pressure (mmHg)	126.2 ± 14.4	131.5 ± 15.1	126.8 ± 11.6	0.25
Diastolic blood pressure (mmHg)	77.1 ± 9.5	75.2 ± 11.4	78.9 ± 8.2	0.35
Hemoglobin (g/L)	112.5 ± 10.9	113.7 ± 15.1 ^{###}	134.9 ± 26.9 ^{△△△}	<0.001
Serum creatinine (μmol/L)	898.1 ± 242.8	816.4 ± 310.9 ^{###}	205.9 ± 165.2 ^{△△△}	<0.001
Serum albumin (g/L)	38.2 ± 3.5 [*]	39.9 ± 4.03 [#]	42.1 ± 3.9 ^{△△△}	<0.001
Serum calcium (mmol/L)	2.36 ± 0.19	2.33 ± 0.19	2.26 ± 0.19	0.07
Serum phosphate (mmol/L)	1.56 ± 0.39	1.61 ± 0.59 ^{###}	1.20 ± 0.24 ^{△△△}	<0.001
Serum potassium (mmol/L)	4.36 ± 0.65 ^{***}	5.14 ± 0.87 ^{###}	4.19 ± 0.52	<0.001
Serum sodium (mmol/L)	138.8 ± 3.4	138.0 ± 0.3 [#]	140.4 ± 3.6 [△]	0.02
Intact parathyroid hormone (pg/mL)	142.2 (63.3-277.1) [*]	215.9 (114.9-449.4) ^{###}	55.2 (37.7-99.7) ^{△△△}	<0.001
High-sensitivity C-reactive protein (mg/L)	2.9 (1.4-7.7)	3.9 (0.7-6.7) [#]	1.0 (0.3-1.8)	<0.001
Triglyceride (mmol/L)	2.6 ± 1.8	1.9 ± 1.4	1.9 ± 0.9	0.06
Total cholesterol (mmol/L)	4.8 ± 1.3 [*]	4.2 ± 0.9	4.5 ± 1.1	0.04
Kt/V (L/w for PD, L/session for HD)	1.9 (1.7-2.2)	1.45 (1.3-1.7)	NA	NA

PD, peritoneal dialysis; HD, hemodialysis; CKD, chronic kidney disease; NA, not applicable. ^{*}P < 0.05, ^{**}P < 0.01, ^{***}P < 0.001, PD vs. HD group; [#]P < 0.05, ^{##}P < 0.01, ^{###}P < 0.001, HD vs. CKD group; [△]P < 0.05, ^{△△}P < 0.01, ^{△△△}P < 0.001, CKD vs. PD group; [&]P between groups

The inter-observer kappa coefficient in the assessment of brain morphological changes was 0.83, indicating good inter-observer agreement. Brain morphologic changes were compared between case-matched PD, HD, and non-dialyzed CKD. The white matter grade, sulcal grade, ventricular grade, and prevalence of SVI were highest in HD patients, followed by PD and non-dialyzed CKD patients ($P < 0.05$). PD and non-dialyzed CKD patients were similar with regard to white matter grade, cerebral atrophy, and prevalence of SVI. The prevalence of hippocampal atrophy and LVI was not significantly different between the groups ($P > 0.05$) (Table 3).

Associations between Cognitive Function and Structural Neuroimaging Findings

Associations between scores of general and specific cognitive domains and brain morphological changes were examined by Spearman analyses; data for all patients were considered together since there were similar trends in all three groups (data not shown separately). White matter grade, ventricular and sulcal grade, and hippocampal size were negatively correlated with the scores for general cognitive function, with correlation coefficients of -0.21 to -0.36 ($P < 0.05$). White matter grade, ventricular grade, hippocampal size, and SVI were also associated with longer completion time on Trail A, with correlation

Table 2. Cognitive function of peritoneal dialysis, hemodialysis, and stage 3-5 chronic kidney disease patients

	PD (n = 60)	HD (n = 30)	CKD stage 3-5 (n = 30)	P
3MS (scores)	87.1 ± 8.7	87.8 ± 10.3 [#]	92.6 ± 6.2 ^{△△}	0.02
CI (%)	11 (18.3%)	7 (23.3%)	1 (3.3%)	0.04
Trail A test (seconds)	65 (50-90)	63 (42.5-90.3) ^{##}	45 (33-62) ^{△△}	0.005
Trail B test (seconds)	175 (128-201)	177.5 (146.8-254.8) ^{###}	132 (95.8-160.3) ^{△△△}	0.001
Executive dysfunction (%)	20 (33.3%)	13 (43.3%) [#]	4 (13.3%) [△]	0.04
Immediate memory (scores)	74.3 ± 15.8	76.9 ± 19.9	84.4 ± 16.9 ^{△△}	0.046
Immediate memory impairment (%)	48 (80%)	20 (66.7%)	20 (66.7%)	0.24
Delayed memory (scores)	94.9 ± 11.8	94.3 ± 17.9 [#]	105.3 ± 9.9 ^{△△△}	0.002
Delayed memory impairment (%)	15 (25%)	11 (36.7%) [#]	4 (13.3%)	0.12
Visuospatial ability (scores)	16.6 ± 3.4	17.0 ± 2.5 ^{###}	19.2 ± 0.9 ^{△△△}	<0.001
Visuospatial impairment (%)	19 (31.7%)	11 (36.7%) ^{##}	2 (6.7%) ^{△△}	0.02
Language ability (scores)	95.6 ± 11.8	98.7 ± 14.3	99.1 ± 9.2	0.36
Language impairment (%)	17 (28.3%)	5 (17.2%)	7 (23.3%)	0.55

PD, peritoneal dialysis; HD, hemodialysis; CKD, chronic kidney disease. **P* < 0.05, ***P* < 0.01, ****P* < 0.001, PD vs. HD group; [#]*P* < 0.05, ^{##}*P* < 0.01, ^{###}*P* < 0.001, HD vs. CKD group; [△]*P* < 0.05, ^{△△}*P* < 0.01, ^{△△△}*P* < 0.001, CKD vs. PD group; &*P* between groups

Table 3. Brain morphologic changes of peritoneal dialysis, hemodialysis, and stage 3-5 chronic kidney disease patients

	PD (n = 60)	HD (n = 30)	CKD stage 3-5 (n = 30)	& <i>P</i>
White matter grade	2.2 ± 1.3 ^{***}	3.6 ± 2.1 ^{###}	1.6 ± 0.9	<0.001
Cerebral atrophy	-	-	-	-
Sulcal grade	2.7 ± 1.3 ^{**}	3.7 ± 1.8 ^{##}	2.7 ± 1.3	0.01
Ventricular grade	2.9 ± 1.3 [*]	3.7 ± 1.9 [#]	2.7 ± 1.5	0.05
Hippocampal atrophy (%)	43 (71.7)%	19 (63.3%)	20 (63.3%)	0.61
Small-vessel infarct (%)	10 (16.7%) ^{**}	15 (50%) [#]	6 (20%)	0.004
Large-vessel infarct (%)	1 (1.67%)	1 (3.33%)	1 (3.33%)	0.87

PD, peritoneal dialysis; HD, hemodialysis; CKD, chronic kidney disease. **P* < 0.05, ***P* < 0.01, ****P* < 0.001, PD vs. HD group; [#]*P* < 0.05, ^{##}*P* < 0.01, ^{###}*P* < 0.001, HD vs. CKD group; [△]*P* < 0.05, ^{△△}*P* < 0.01, ^{△△△}*P* < 0.001, CKD vs. PD group; &*P* between groups

coefficients of -0.21 to -0.36 (*P* < 0.05). White matter grade was also associated with lower scores for immediate and delayed memory, and visuospatial and language abilities, with correlation coefficients of -0.24 to -0.35 (*P* < 0.01) (Table 4).

Older age; lower level of education; presence of DM; higher phosphate, creatinine, and hs-CRP levels; and lower hemoglobin, serum albumin, and serum sodium values were all significantly associated with lower scores for general cognitive function and at least two domains of specific cognitive function (*P* < 0.05). There were no associations between any of the items of CI and CVD history or serum levels of calcium, uric acid, potassium, iPTH, and lipids (*P* > 0.05).

When global and specific CIs were examined as categorical variables, higher white matter grade, ventricular grade, and hippocampal atrophy were significantly associated with general CI. In multivariate analysis, after adjustment for recognized influence factors [29, 30], include age, education, CVD history, DM, serum albumin, and serum sodium levels, these neuroimaging findings still independently predicted a higher risk for global CI, with a hazard ratio (HR) of 1.80 (1.22-2.64), 1.67 (1.09-2.57), and 2.49 (1.07-5.77), respectively.

Table 4. Correlation coefficients of scores of general and specific cognitive function, brain morphological changes and clinical data by Spearman analysis for the whole cohort

	3MS	Trail A	Immediate memory	Delayed memory	Visuospatial ability	Language ability
White matter grade	-0.36***	0.36***	-0.29**	-0.32**	-0.35**	-0.24*
Sulcal grade	-0.25*	0.17	-0.17	-0.11	-0.10	-0.17
Ventricular grade	-0.27**	0.21*	-0.22*	-0.16	-0.16	-0.22*
Hippocampal size	-0.21*	0.21*	-0.12	-0.06	-0.17	-0.17
Small-vessel infarct	-0.17	0.30**	-0.15	-0.14	-0.18	-0.13
Age	-0.27**	0.32**	-0.24*	-0.10	-0.16	-0.15
Gender	-0.13	0.19	-0.05	-0.02	-0.17	-0.04
Education	0.36**	-0.42**	0.30**	0.32**	0.35**	0.31**
Diabetes	-0.24*	0.41**	-0.20*	-0.24*	-0.17	-0.16
Cardiovascular disease	-0.12	0.15	-0.08	-0.13	-0.16	-0.16
Serum phosphate	-0.18	0.26**	-0.20*	-0.31**	-0.16	-0.17
Serum creatinine	-0.24*	0.32**	-0.16	-0.28**	-0.31**	-0.21*
Hs-CRP	-0.30**	0.38**	-0.26**	-0.15	-0.32**	-0.23*
Hemoglobin	0.18	0.30**	0.17	0.17	0.28**	0.11
Serum albumin	0.23*	-0.23*	0.15	0.24*	0.30**	0.06
Serum sodium	0.22*	-0.30**	0.15	0.12	0.27*	0.21*

Hs-CRP, high-sensitivity C-reactive protein. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Table 5. Association of brain morphologic changes and general, specific cognitive impairment by univariate and multivariate logistic regression analysis for the whole cohort

	General CI		Executive dysfunction		Immediate memory impairment		Delayed memory impairment		Visuospatial ability impairment		Language ability impairment	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
White matter grade												
Unadjusted	1.75 (1.29-2.38)	<0.001	1.64 (1.19-2.25)	0.002	1.09 (0.81-1.47)	0.56	1.56 (1.15-2.12)	0.004	1.43 (1.09-1.88)	0.11	1.28 (0.97-1.70)	0.08
Adjusted*	1.80 (1.22-2.64)	0.003	1.43 (0.96-2.15)	0.08	1.13 (0.76-1.70)	0.54	1.63 (1.12-2.39)	0.01	1.14 (0.79-1.64)	0.48	1.07 (0.76-1.51)	0.71
Sulcal grade												
Unadjusted	1.41 (1.03-1.95)	0.04	1.38 (1.02-1.88)	0.03	0.93 (0.68-1.26)	0.65	1.26 (0.93-1.72)	0.14	1.24 (0.92-1.68)	0.16	1.16 (0.84-1.59)	0.35
Adjusted*	1.35 (0.91-2.01)	0.14	1.15 (0.75-1.74)	0.53	0.90 (0.60-1.34)	0.60	1.23 (0.83-1.82)	0.31	0.94 (0.62-1.42)	0.76	0.91 (0.60-1.36)	0.64
Ventricular grade												
Unadjusted	1.60 (1.15-2.23)	0.005	1.43 (1.06-1.92)	0.02	0.97 (0.73-1.30)	0.85	1.36 (1.01-1.84)	0.04	1.21 (0.91-1.62)	0.19	1.21 (0.89-1.64)	0.21
Adjusted*	1.67 (1.09-2.57)	0.02	1.26 (0.83-1.91)	0.28	0.96 (0.65-1.42)	0.83	1.37 (0.94-2.02)	0.11	0.90 (0.60-1.35)	0.60	0.98 (0.67-1.45)	0.93
Hippocampal atrophy												
Unadjusted	2.12 (1.15-4.21)	0.03	1.85 (0.97-3.51)	0.08	0.69 (0.36-1.32)	0.26	1.26 (0.65-2.42)	0.49	1.28 (0.67-2.43)	0.46	1.22 (0.62-2.39)	0.57
Adjusted*	2.49 (1.07-5.77)	0.03	1.25 (0.49-3.17)	0.64	0.58 (0.25-1.34)	0.21	0.96 (0.43-2.18)	0.93	0.83 (0.34-2.02)	0.68	0.73 (0.31-1.73)	0.48
Small-vessel infarct												
Unadjusted	3.45 (1.22-9.75)	0.02	4.49 (1.69-11.9)	0.003	0.75 (0.27-2.03)	0.57	2.36 (0.88-6.30)	0.08	3.11 (1.18-8.18)	0.02	1.89 (0.67-5.32)	0.23
Adjusted*	2.48 (0.72-8.55)	0.15	2.37 (0.57-9.79)	0.23	0.46 (0.13-1.68)	0.24	1.90 (0.56-6.38)	0.30	1.30 (0.40-54.97)	0.70	0.82 (0.22-3.10)	0.77

*After adjustment for age, education, diabetes, CVD history, serum albumin, and sodium.

After multivariate adjustment, white matter grade was also independently associated with impaired delayed memory, with a HR of 1.63 (1.12-2.39). Although higher sulcal grade and SVI were associated with a higher risk for general CI, this association disappeared after multivariate adjustment. In addition, sulcal grade, ventricular grade, and SVI were associated with executive dysfunction and impairment of delayed memory or visuospatial ability on univariate regression analyses, but these associations disappeared after multivariate adjustment (Table 5).

Discussion

Our data indicate that both PD and HD patients performed worse than non-dialyzed CKD patients in global and most specific cognitive functions (the exception being language ability). However, our study showed no differences in general CI and the major cognitive domains between case-matched PD and HD patients. This is different from the previous studies, which have indicated that the prevalence of general CI is lower in PD than in HD patients [9, 10]. One study reported the comparable rates of CI between HD and PD but PD patients have more severe impairment in immediate memory and less impairment in executive dysfunction than HD patients [3].

Previous studies have shown that anatomic changes such as cerebral atrophy, white matter hyperintensities, and silent infarction in both HD [5, 6] and PD patients [7, 8], but there have been few comparisons between the two groups. Our data showed that HD patients have more severe neuroimaging abnormalities (white matter grade, sulcal and ventricular grade, and SVI) than PD and non-dialyzed CKD patients, with the latter two having comparable prevalence of abnormalities. Of note, HD patients were at higher risk for severe hyperphosphatemia, hyperparathyroidism, and inflammation in this study. Whether these would result in a higher prevalence of SVI and WMH needs to be explored [31]. Secondly, HD treatment per se contributes to intra-hypotension, dialysis disequilibrium, and intra-dialytic fluctuation of extracellular volume, which might be responsible for the more severe anatomic brain disease [32]. As previous studies have shown, HD patients have lower cerebral blood flow, with low cerebral oxygenation levels, during the interdialytic cycle than PD patients [12]. Computerized tomography has demonstrated significant decrease in brain density (compared to the normal) during and after HD, but this has not been seen in PD patients [11]. Since both cerebral infarcts and white matter disease are associated with higher future stroke risk [33, 34], regular MRI examination may be particularly important for HD patients.

The association between CI and neuroimaging abnormalities in the general population is well known [13-15], but there are few studies in CKD patients [6, 19, 35]. Although CVD risk factors are commonly recognized as the link between brain morphological changes and CI [4, 16, 17], our data indicate a high prevalence of general and specific CI coupled with a high burden of neuroimaging abnormalities in CKD patients without history of stroke. Further, the association of global CI with WMH and cerebral atrophy was independent of CVD history and CVD risk factors for the whole CKD group. These findings might be supported by previous studies indicating that CKD, per se, contributes to cognitive decline [36], independent of ischemic cerebral lesions [35], and that HD is associated with CI, independent of CVD risk factors, SVI, and brain atrophy [37]. Indeed, white matter lesions, which were shown to be a strong predictor of general CI in our study, could be present not only in stroke but also in multiple sclerosis [38], pyridoxine deficiency, and cerebral metabolic disturbances in CKD patients [18]. Also, nonvascular anatomic disease, such as brain degeneration of toxic-metabolic etiology, may be associated with CI in this population. Taken together, our findings support the theory that the mechanism of CI in CKD might be independent of CVD [39].

It is of interest that HD patients had worse neuroimaging abnormalities but comparable cognitive function with case-matched PD patients according to our data. The potential mechanism for this phenomenon is not clear. Our HD patients had severe hyperphosphatemia, hyperparathyroidism, and inflammation in this study. The extent of fluctuations in fluid and solute removal in relation to dialytic treatment significantly varied for PD and HD. Family and social support, psychological issues, and rehabilitation status also might differ between these two groups. The potential influence of these factors on global and specific CI has to be clarified in future studies with large samples.

This study has several strengths. There are few previous studies comparing the CI and neuroimaging abnormalities between case-matched PD, HD and non-dialyzed CKD. In this study, to avoid confounding, we case-matched patients for selected variables, including age, gender, educational level, diabetes status, and dialysis duration (where appropriate). Our

cognitive battery included a wide range of tests to assess a broad spectrum of cognitive domains. Brain morphological changes were assessed in detail by the same neuroradiologists using a semi-quantitative scoring system. Recognized confounders for CI in the general population and in patients on dialysis were factored into the multivariable linear and logistic regression models.

Our study also had some limitations. First, due to the cross-sectional nature of the study, we cannot determine whether the neuroimaging findings are pathogenic factors of CI or just concomitant phenomena. Functional MRI might be able to clarify this. Second, our study participants were all Chinese speaking, which limits the generalizability of our results. Finally, this was a single-center study with a small sample size.

Conclusion

Our study shows that while renal function plays an important role in the risk of CI, dialysis modality does not influence global or specific cognitive functioning. However, HD patients have more severe neuroimaging abnormalities than PD and non-dialyzed CKD patients. WMH and cerebral atrophy indicate higher risk for global CI, independently of CVD and CVD risk factors. Future studies could examine nonvascular as well as vascular disease modification strategies in individuals requiring dialysis with cognitive impairment.

Disclosure Statement

The authors declare that they have no conflict of interest. And the results presented in this paper have not been published previously in whole or part, except in abstract format.

Acknowledgments

The authors would like to express their appreciation to the patients, doctors, and nursing staff of the Peritoneal Dialysis Center of Peking University First Hospital, Department of Radiology of Peking University First Hospital, who participated in this study. This study was in part supported by the New Century Excellent Talents from Education Department of China, the Baxter Clinical Research Award from Baxter Corp of China, and ISN Research Award from ISN GO R&P Committee. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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