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ORIGINAL ARTICLE

Cerebral blood flow changes in hemodialysis and peritoneal dialysis patients: an arterial-spin labeling MR imaging

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Abstract We used arterial-spin labeling (ASL) MR imaging, a non-invasive technique to evaluate cerebral blood flow (CBF) changes in patients with end-stage renal disease (ESRD) undergoing peritoneal dialysis (PD) and hemodialysis (HD), and nondialysis ESRD patients compared with healthy cohort. Ninety seven ESRD patients including 32 PD patients (20 male, 12 female; mean age 33 ± 8 years), 33 HD patients (22 male, 11 female; mean age 33 ± 8 years) and 32 nondialysis patients (20 male, 12 female; mean age 35 ± 7 years) and 31 age- and gender-matched healthy controls (20 male, 11 female; mean age 32 ± 8 years) were included in this study. All subjects underwent ASL MR imaging, neuropsychologic tests, and ESRD patients underwent laboratory testing. CBF values were compared among PD, HD, nondialysis patients and control groups. Correlation analysis and multiple regression analysis were performed to investigate the association between CBF values and hemoglobin, neuropsychologic test results, serum creatinine, urea levels, disease duration, and dialysis duration. Elevated CBFs of whole brain region, gray matter, and white matter were found in all ESRD patient groups compared with healthy controls (all $P < 0.001$). However, compared with non-dialysis ESRD patients, both PD and HD patients had widespread regional CBF decline mainly in bilateral frontal and anterior cingulate cortices. There were no differences for CBF between PD and HD patient groups. Negative correlations were observed between mean CBFs of whole brain region, gray matter, and white matter and the hemoglobin level in all ESRD patients. Multiple linear regression showed elevated CBF of multiple brain areas correlated with some neuropsychological tests in ESRD patients (all $P < 0.001$, AlphaSim corrected), but the association was not present or shrank after adjusting hemoglobin level. This study found that mean CBF was predominantly increased in patients with ESRD, which correlated with their hemoglobin level and neurocognitive disorders. There were no differences of CBF change and cognitive function between PD and HD ESRD patients with long-term treatment. The degree of anemia may be a predominant risk factor for cognitive impairment in these ESRD patients.

Keywords End-stage renal disease (ESRD) · Cerebral blood flow (CBF) · Peritoneal dialysis (PD) · Hemodialysis (HD) · Arterial-spin labeling (ASL)

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Abbreviations

ASL	Arterial-spin labeling
CBF	Cerebral blood flow
DST	Digit-symbol test
ESRD	End-stage renal disease
NCT-A	Number connecting-A
PD	Peritoneal dialysis
HD	Hemodialysis

Introduction

End-stage renal disease (ESRD) has become a severe global burden on health and economic output in the last decades, especially in developing nations (Eknoyan et al. 2004; Nugent et al. 2011). It is defined as chronic renal failure with a glomerular filtration rate (GFR) < 15 mL/min/1.73m^2, or kidney function progressed to the point at which permanent replacement therapy is required. Both hemodialysis (HD) and peritoneal dialysis (PD) are common treatment modalities for ESRD patients. Cognitive impairments are common in both HD and PD patients (Murray et al. 2006; Kalirao et al. 2011). Multiple potential risk factors may contribute to cognitive impairments and have been reported in previous studies, such as high prevalence of cardiovascular disorders (Knopman et al. 2001; Nakatani et al. 2003), uremia (Arieff 1985) and anemia (Marsh et al. 1991). Different from west countries, cerebral hyperperfusion and increased risk of hemorrhage stoke among dialysis patients were reported in the Japanese population (Seliger et al. 2003; Iseki and Fukiyama 1996). Also, cerebrovascular disease is one of the leading causes of death among dialysis patients in China (Yao et al. 2009). It is possible that high risk of cerebrovascular diseases in ESRD population of east Asia is related with cerebral hyperperfusion. Thus, it is important to understand the effect of dialysis on the cerebral circulation.

Medical imaging plays an important role on detecting changes in cerebral circulation in patients with ESRD. Several previous studies focused on the changes in cerebral blood flow (CBF) in HD patients using various kinds of imaging techniques, such as arterial spin labeling (ASL) MRI (Prohovnik et al. 2007), transcranial Doppler ultrasonography (Hata et al. 1994), computed tomography (Vorstrup et al. 1992), positron emission tomography (PET) (Kuwabara et al. 2002), and single photon emission computed tomography (SPECT) (Fazekas et al. 1996; Isshiki et al. 2014), and these results were not coincidental depending on the population studied and the assessment methodology. For example, Vorstrup et al. and Kuwabara et al. reported an increase in CBF in anemic patients on long-term hemodialysis, while Prohovnik et al. investigated the circulatory pathophysiology of HD patients without anemia, and they found HD patients had very low interdialytic cerebral perfusion, which acutely normalizes after each hemodialysis treatment.

In contrast to HD, PD has been considered to exert little significant hemodynamic change and fluctuations in body fluid content (McIntyre 2011). Moreover, Some previous studies demonstrated that ESRD patients treated with PD appeared to be less likely to develop hemorrhagic stroke than those treated with HD (Toyoda et al. 2005; Wang et al. 2014), indicating that PD might have different effects on cerebral circulation compared with HD. However, less has been done to study cerebral perfusion in ESRD patients undergoing PD and compare the effect of dialysis modality on cerebral perfusion between the patients receiving HD and PD treatment.

The purpose of this study was to investigate the effect of dialysis modality on the CBF and cognitive function in ESRD patients with receiving PD and HD treatment. To ensure the reliability of the result, we included those ESRD patients without any dialysis treatment as positive controls.

Materials and methods

Subjects

All participants provided written consent forms before the study. Until March 2016, a total of 127 patients with ESRD were recruited, including 46 patients undergoing PD (PD group), 39 patients undergoing HD (HD group) and 42 ESRD patients without any dialysis treatment (nondialysis group). Patient inclusion criteria were as follows: (1) older than 18 years in age, (2) disease duration of greater than 3 months for all patients with ESRD and regular dialysis duration of greater than 6 months for patients undergoing PD or HD. (3) No any MRI contraindications, (4) They can finish neuropsychological tests. Exclusion criteria were as follows: (1) patients who have received another dialysis therapy for longer than 3 months, (2) patients with other brain diseases including cerebral infarct, trauma, and tumors that affect brain functions, (3) patients with other chronic system disease or diseases potentially affecting brain function, (4) head motion greater than 1.0 mm or 1.0° during MR imaging. Among PD patients, 4 patients were transferred to HD therapy, 4 patients were of other concomitant chronic system disease (2 Hepatitis B, 2 diabetes mellitus), one patient had inadequate brain ASL images, and 5 patients had head motion more than 1.0 mm or 1.0°. Among HD patients, 3 patients had concomitant chronic system disease (1 systemic lupus erythematosus disease, 2 diabetes mellitus), one patient had inadequate brain ASL images, and 2 patients had marked head motion. Among nondialysis patients, 2 patients had congenital disorder (tetralogy of Fallot and absence of left kidney, n = 1 for each), 3 patients had inadequate brain ASL images, and 5 patients had marked head motion. Hence, 14 PD, 6 HD and 10 nondialysis patients were excluded. The remaining 32 PD patients (20 male, 12 female; mean age 33 ± 8 years), 33 HD patients (22 male, 11 female; mean age 33 ± 8 years) and 32 nondialysis patients (20 male, 12 female; mean age 35 ± 7 years) were included in the final data analysis.

Thirty-one age- and gender-matched healthy controls (HCs) (20 male, 11 female; mean age 32 ± 8 years) were recruited from the local community. All the volunteers were more than 18 years old without abnormal findings in abdominal ultrasonographic imaging. They had also no diseases of the kidney or other systems and no history of neuropsychiatric

symptoms. Other exclusion criteria were the same as ESRD patients.

Clinical evaluation and laboratory examinations

Patients' medical records were reviewed by one author (X.L.J.), and related information including disease duration, dialysis modality, dialysis duration were extracted. Blood samples were collected within one day before MR scanning and were analyzed at the clinical laboratory of Jinling Hospital. Routine blood test was performed in all subjects. Additional blood tests, including serum creatinine, and urea were measured in ESRD patients.

Neuropsychological tests

All subjects conducted a battery of neuropsychological tests, including the number connecting A test (NCT-A), digit symbol test (DST), line-tracing test (LTT), serial dotting test (SDT) and self-rating depression scale (SDS). These neuropsychological tests were used to assess psychomotor speed, attention, visual memory and depression level (Bajaj et al. 2009).

Imaging data acquisition and analysis

The pseudo continuous arterial spin labeling (pCASL) sequence was provided by the center for functional neuroimaging, University of Pennsylvania, USA. The imaging parameters were as follows: slice thickness = 5 mm, slices =18, TR = 4000 ms, TE = 12 ms, band width = 3126 Hz, flip angle =90^o, measurements =90, post label delay =1200 ms, and label offset =90 mm. The pCASL data processing are based on the ASL Data Processing Toolbox (ASLtbx,http://www.cfn.upenn.edu). First, the ASL images were preprocessed by realignment, motion correction, and spatial smoothing with FWHM of 6 mm. Second, perfusion difference images were calculated by sinc subtraction of the label/control pairs. The quantification method to obtain relative mean CBFs of the gray matter, white matter and the whole brain regions was based on published quantification model (Wang et al. 2005). Third, relative CBF map of each subject was normalized to the standard Montreal Neurological Institute (MNI) template provided by SPM8 (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl. ac.uk) and smoothed using FWHM of 6 mm before group-level analysis.

Statistical analysis

Software SPSS version 16.0 (SPSS Inc. Chicago, IL, USA) was used to analyze the demographic data, neuropsychological tests, and biochemical data. χ^2 test was used to analyze sex distribution among ESRD patients groups and healthy group. One-way analysis of variances (ANOVA) test was used to investigate the differences in disease duration, blood biochemistry tests and neuropsychologic test results among patients and healthy control group. Pearson correlation analysis was performed to display the correlation between mean CBF values and hemoglobin, neuropsychologic test results, serum creatinine, urea levels, disease duration, and dialysis duration. All P values less than 0.05 were regarded as statistically significant.

To evaluate the mean CBF changes in ESRD patients, the gray matter, white matter and the whole brain regions were defined as ROIs based on SPM8 templates. Voxel-wise CBF maps were analyzed by SPM8 to explore the regional CBF differences among the three groups (PD, HD and nondialysis patients). Results were corrected by Monte Carlo simulation software with a P value less than 0.01 considered indicative of a significant difference, and a cluster size greater than 341 mm^3, which corresponded to a corrected P value of less than 0.05. Monte Carlo simulation were imported with the following parameters: voxel size, 1.5*1.5*1.5 mm^3; full width at half maximum, 6 mm. Post-hoc analysis was further performed for inter-group comparisons if a significant difference was present. A multiple regression analysis was used to analyze the correlation between CBF values in all ESRD patients and neuropsychologic test scores in SPM8. Age and sex were included as covariates in this analysis in ModelI. To control confounding variable of hemoglobin level, Hb was further included as a covariate into the multiple regression analyses in Model II. An AlphaSim corrected P value less than 0.001 was regarded as statistically significant.

Results

Demographic data and laboratory findings for patients with ESRD and HCs are listed in Table 1. No significant difference was found in age and gender among patients and healthy control groups (all $P > 0.05$). The difference of hypertension, disease duration and dialysis duration among the ESRD patients group did not reach the statistical significance (all $P > 0.05$), while higher hemoglobin level, higher serum creatinine values and lower urea level were found in both PD and HD group than those in the nondialysis group ($P < 0.05$). Compared to HCs, patients with ESRD had worse performance of DST, NCT-A and SDS (all $P < 0.05$).

Patients with ESRD showed significantly higher mean CBFs of whole brain region (51.62 ± 9.69 mL/100 g/min), gray matter (54.85 ± 10.25 mL/100 g/min), and white matter (35.00 ± 7.37 mL/100 g/min) than those in healthy controls (37.93 ± 4.29 mL/100 g/min for whole brain, 40.44 ± 4.57 mL/100 g/min for gray matter, and 24.96 ± 3.30 mL/100 g/min for white matter, respectively) (all $P < 0.001$). Voxel-level ANOVA results showed that CBF was significantly different among the three ESRD

Table 1 Demographic and laboratory data of end-stage renal disease patients and healthy control subjects

Variables	Healthy control (n = 31)	Nondialysis (n = 32)	PD (n = 32)	HD (n = 33)
Age (Y)	32 ± 8	35 ± 7	33 ± 8	33 ± 8
Gender (M/F)	20/11	20/12	20/12	22/11
Hypertension	-	14/32	17/33	15/33
Disease duration (mo.)	-	49 ± 51	52 ± 46	52 ± 49
Dialysis duration (mo.)	-	-	22 ± 13	19 ± 14
Blood biochemistry tests				
Hemoglobin (g/L)		86 ± 20	92 ± 16	99 ± 17
Creatinine (μmol/L)	-	727 ± 206	1107 ± 333	918 ± 265
Urea (mmol/L)	-	24 ± 8	20 ± 6	19 ± 6
Neuropsychologic tests				
NCT-A (sec)	33 ± 13	42 ± 12	40 ± 11	42 ± 14
DST (score)	65 ± 14	52 ± 14	57 ± 11	57 ± 14
LTT (sec)	53 ± 18	58 ± 19	55 ± 24	52 ± 19
SDT (sec)	48 ± 15	51 ± 18	48 ± 13	47 ± 13
SAS (score)	37 ± 8	40 ± 9	39 ± 9	38 ± 9
SDS (score)	37 ± 8	42 ± 10	41 ± 9	41 ± 8

Data are expressed as means ± standard deviation

PD = peritoneal dialysis; HD = hemodialysis; NCT-A = number connection test-A; DST = digital symbol test; LTT = line-tracing test; SDT = serial-dotting test; SAS = self-rating anxiety scale; SDS = self-rating depression scale

patients groups in multiple gray matter areas (Fig. 1). Compared to nondialysis group, PD patients displayed lower CBF in the bilateral frontal, middle temporal lobes and anterior cingulate cortex, HD group displayed lower CBF in the bilateral frontal and insula lobes, anterior cingulate cortex, right precuneus and left occipital lobes (Fig. 1, Table 2) ($P < 0.01$, AlphaSim corrected), while the brain regions with statistical difference were not observed between PD and HD groups.

Figure 2 illustrates the correlations between mean CBFs and hemoglobin level in all ESRD patients. Mean CBFs of ESRD patients showed negative correlations with hemoglobin levels (global CBF: $r = -0.698$, $P < 0.001$; gray matter CBF: $r = -0.698$, $P < 0.001$; white matter CBF: $r = -0.643$, $P < 0.001$). Voxel-level correlations between CBF and the neuropsychologic test scores in ESRD patients are displayed in Fig. 3 ($P < 0.001$, AlphaSim corrected). Age and sex were adjusted in ModelI. DST was negatively associated with CBF of bilateral temporal,parietal lobes, anterior cingulate cortex and left insula. SDS positively correlated with CBF of bilateral temporal lobes, right frontal lobe and hippocampus. SAS positively correlated with CBF of right putamen and insula, right frontal lobe, bilateral temporal lobes. Hb level was further included as a covariate to control confounding variables

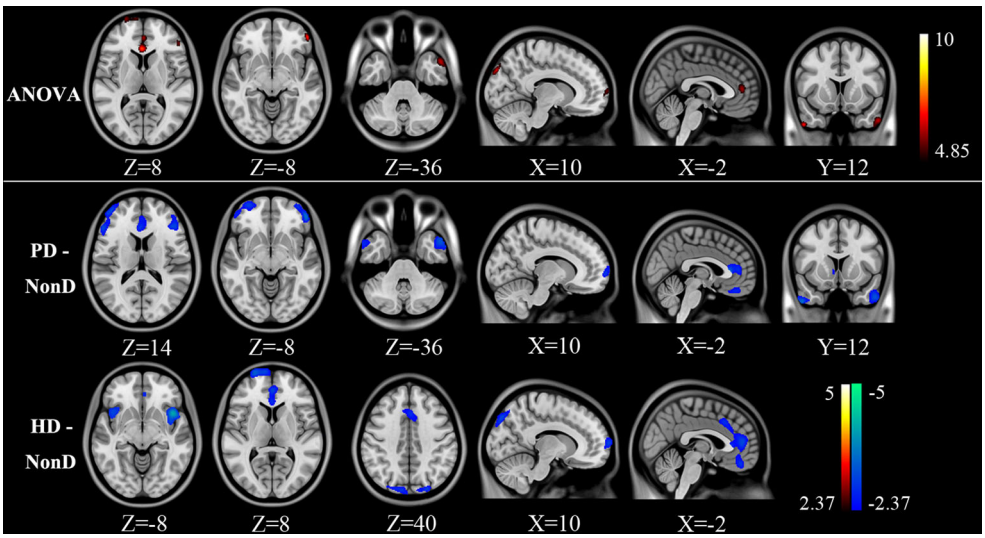

Fig. 1 Cerebral blood flow differences among PD, HD, and nondialysis (NonD) groups ($P < 0.01$, AlphaSim corrected). Compared with nondialysis group, patients in PD group display lower CBF in the bilateral frontal, middle temporal lobes and anterior cingulated cortex, HD group displays lower CBF in the bilateral frontal and insula lobes, anterior cingulated cortex, right precuneus and left occipital lobe, while brain regions with statistical difference are not observed between PD and HD groups

Table 2 Regions shows CBF differences between PD/HD group and nondialysis group

Brain Regions	MNI Coordinates (mm)			Volume	Peak
	x	y	z	(mm^3)	t value
PD group vs. *nondialysis group*					
Right middle frontal gyrus	39	57	24	2667	3.54
Left middle frontal gyrus	−50	45	−6	1418	3.63
Right inferior frontal gyrus	54	31	21	657	3.48
Left inferior frontal gyrus	−50	39	8	1195	3.32
Right superior frontal gyrus	29	64	35	1308	2.61
Right middle temporal gyrus	51	12	−43	339	3.59
Left middle temporal gyrus	−48	7	−42	515	3.47
Anterior cingulate cortex	−2	43	11	939	2.86
HD group vs. *nondialysis group*					
Right precuneus	9	−85	45	514	3.20
Right superior frontal gyrus	26	67	6	447	3.34
Left superior frontal gyrus	−20	49	−20	375	3.51
Left medial frontal gyrus	−6	44	−17	535	2.99
Left occipital lobe	−30	87	32	626	3.34
Right insula	39	19	−9	502	2.82
Left insula	−44	15	−6	728	4.02
Anterior cingulate cortex	0	46	11	796	3.17

CBF = cerebral blood flow; MNI = Montreal Neurological Institu

in ModelII ($P < 0.001$, AlphaSim corrected). After adjustment for hemoglobin level, the association between CBF and SAS, SDS scores were not present, while the brain regions correlated with DST remarkably shrank.

Discussion

The present study demonstrated increased CBF values in ESRD patients compared with healthy controls, which correlated with their hemoglobin level and neurocognitive disorders. While the effects of the two modalities of chronic dialysis treatment (PD and HD) on cerebral perfusion and cognitive function were not different from each other.

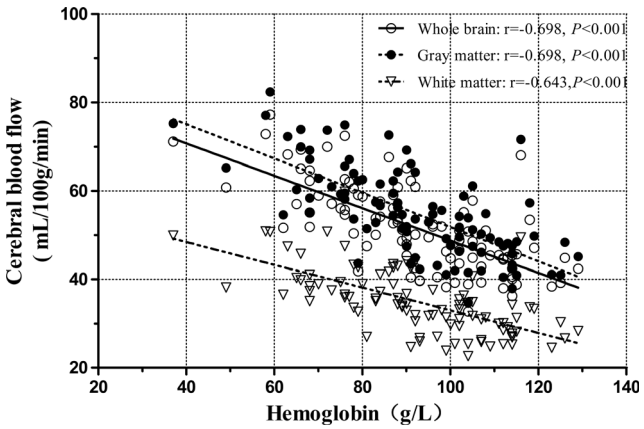

Fig. 2 The hemoglobin level of ESRD patients negatively correlates with whole brain cerebral blood flow (CBF) (*open circles*), gray matter CBF (*closed circles*), and white matter CBF (*triangle*)

In our study, we found diffusely increased CBF of ESRD patients compared with healthy controls. The abnormal CBF of ESRD patients correlated with neuropsychologic test results such as DST, SAS and SDS, which suggested disturbances in memory, psychomotor speed, attention and emotion. The findings were supported by previous studies based on other neuroimaging techniques, such as resting-state functional MR imaging (Ni et al. 2014; Zheng et al. 2014; Luo et al. 2015), voxel-based morphometry (Zhang et al. 2013; Chai et al. 2015) and diffusion-tensor imaging (Kong et al. 2014). The above neuroimaging results demonstrated that patterns of brain functional and structural abnormalities in ESRD patients, including functional connectivity impairments, cerebral atrophy and white matter integrity disruptions, were potential pathophysiological mechanisms underlying cognitive dysfunction in ESRD patients.

A significant inverse correlation was observed between mean CBF and the hemoglobin level. This finding was consisted with previous reports using CT (Vorstrup et al. 1992; Mathew et al. 1985) and PET (Hirakata et al. 1992). The mechanism can be explained by both brain tissue hypoxia and a reduction of cerebral vasodilatory capacity, which one works more dominantly remains controversial (Kuwabara et al. 2002). Earlier studies showed that cerebral vasodilation is the more important factor contributing to the preservation of

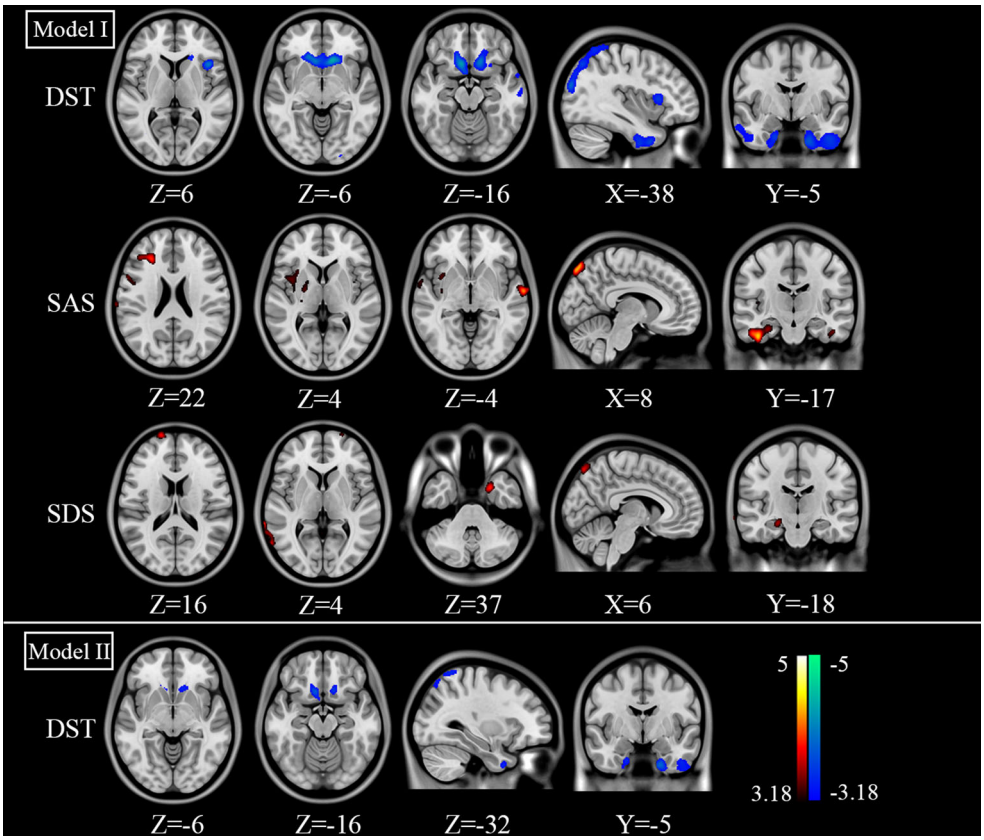

Fig. 3 Correlations between cerebral blood flow values and neuropsychologic test scores in end-stage renal disease patients ($P < 0.001$, AlphaSim corrected). Age and sex are adjusted in ModelI, while hemoglobin level is further adjusted in ModelII

stable oxygen delivery, but some of the CBF increase was due to lowered viscosity (Paulson et al. 1973; Horina et al. 1991). However, another observation demonstrated that hypoxia-induced brain damage may reduce the cerebral vasodilatory capacity (Kuwabara et al. 2002). In our study, elevated CBF of ESRD patients due to anemia correlated with cognitive dysfunction indicated that anemia could be an important contributor to cerebral dysfunction. This assumption was confirmed by several studies that correction of anemia in dialysis patients improved brain and cognitive functions (Marsh et al. 1991; Kambova et al. 1998; Pickett et al. 1999; Temple et al. 1995).

We focused on the effects of PD and HD treatment to cerebral circulation and cognitive function of ESRD patients. Our study showed PD patients had no differences of CBF change or cognitive function compared with HD patients. Although some earlier studies indicated that patients with ESRD undergoing PD had consistently better cognitive function than patients treated with HD (Wolcott et al. 1988; Buoncristiani et al. 1993; Tilki et al. 2004), recent studies demonstrated that there was no difference on cognitive performance between well-dialysed, well-nourished and medically stable HD and PD patients (Radić et al. 2010, 2011). Günal et al. (Günal et al. 2003) found that the effects of HD and PD on long-term control of blood pressure and cardiac structure and function were not different from each other. Although patients undergoing HD experience more interdialytic hemodynamic change, fluctuations in body fluid content than patients undergoing PD, several studies have confirmed that fluctuation in CBF during the interdialytic cycle can normalize at the end of the session (Metry et al. 2002; Prohovnik et al. 2007). The selected HD patients in this study underwent MRI examination at one day after dialysis, so the effect of hemodynamic fluctuation may be not a significant confounding factor. Taken together, these studies supported our findings.

In this study, those dialysis patients had a decreased CBF and improved cognitive function compared to nondialysis patients. Both PD and HD patient groups showed widespread regional CBF decline mainly in bilateral frontal and anterior cingulate cortices. Relatively lower CBF in frontal cortex was also observed in HD patients with anemia in one previous study (Hirakata et al. 1992), which was in line with the hypothesis that the frontal cortex may be more susceptible to blood supply due to some anatomic or hemodynamic factors (Hirakata et al. 1992; Venkateshappa et al. 2012). Anterior cingulate cortex has been implicated in emotional and cognitive processing (Bush et al. 2000). We believe that the decreased CBF of PD patients in above regions may partially interpret these improvements in neurocognitive dysfunctions. It is reported that the increased CBF might contribute to the brain tissue damage through an increased delivery of uremic toxins to the brain tissues (Marsh et al. 1991). Conversely, the relatively low CBF of dialysis patients may reduce the

delivery of uremic toxins to the brain, then an improvement in brain function could be expected. Although the serum creatinine in dialysis patients groups were higher than nondialysis group, previous studies showed that serum creatinine was not a nonspecific indicator of renal failure and had a weak relationship to the pathophysiological process resulting in cognitive dysfunction in uremia patients (Marsh et al. 1986; Madan et al. 2007).

Several limitations of our study should be acknowledged. Firstly, the sample size in our study was relatively small, so the validity of the statistical analysis was limited to demonstrate difference among the groups. Secondly, we cannot clarify the hemodynamic changes in patients with ESRD before and after dialysis, and intradialysis cycle. The best design is to perform a longitudinal study. Finally, we did not address the potential effect of other variables on CBF in patients with ESRD, such as the histopathological type of nephropathy, etc. Further studies are needed.

In conclusion, this study demonstrated predominantly increased CBF in patients with ESRD compared with healthy controls, which correlated with hemoglobin level and neurocognitive dysfunction, however, there was no difference of CBF change or cognitive function between the PD and HD patients on long-term treatment. The degree of anemia can be a predominant risk factor for cognitive impairment in ESRD patients based on the present study. Thus, it appears helpful to study the effect of anemia improvement on CBF and cognitive function changes in ESRD patients.

Compliance with ethical standards

Conflict of interest None.

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