Regional Cerebral Gray Matter Atrophy Is Associated With Cognitive Impairment in Hemodialysis Patients: a Cross-sectional and Longitudinal Voxel-based Morphological Mri Study

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Research Article

Keywords: Kidney Failure, Chronic, Renal Dialysis, Magnetic Resonance Imaging, Gray matter, Cognitive Dysfunction

Posted Date: May 5th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-480949/v1>

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Version of Record: A version of this preprint was published at Brain Imaging and Behavior on January 7th, 2022. See the published version at <https://doi.org/10.1007/s11682-021-00602-9>.

Abstract

To explore changes of cerebral gray matter volumes (GMV) in hemodialysis patients, the clinical risk factors for GMV changes, and the relationship between GMV changes and neuropsychological tests results. Eighty-eight hemodialysis patients and seventy-six healthy controls (HCs) were recruited in this study. Fifty patients underwent follow-up magnetic resonance, blood biochemical examinations, and neuropsychological test (1.75 ± 0.55 years). Changes in GMV between patients and HCs, longitudinal GMV changes in patients were explored. The clinical risk factors for the longitudinal GMV changes, the correlations between longitudinal GMV changes and neuropsychological tests changes in hemodialysis patients were analyzed. Compared to HCs, the hemodialysis patients had diffusely decreased in GMV (with age, sex, and total intracranial volume [TIV] as covariates, $P < 0.001$, voxel-wise threshold false discovery rate [FDR] corrected). Compared with patients at baseline, regional decreased GMV were found in patients at follow-up (with age, and TIV as covariates, $P < 0.05$, voxel-wise threshold FDR corrected). Increased serum urea, parathyroid hormone levels, and hemodialysis duration were independent risk factors for decreased GMV in hemodialysis patients (all $P < 0.05$, FDR corrected). Hemodialysis patients had lower MMSE (27[26, 29]) and MoCA (22[19.48, 24.04]) scores than HCs (30[29, 30] and 28[26.89, 29]) (all $P < 0.05$). The MMSE scores of hemodialysis patients at follow-up (26[25, 28.5]) were lower than those of patients at baseline (28[25, 29.5]) ($P = 0.02$). The decreased left caudate volumes were positively correlated with reduced MMSE scores in hemodialysis patients ($r_s = 0.437$, $P = 0.033$). Hemodialysis patients had diffused GM atrophy over time, which was related to cognitive impairment.

Introduction

Kidney failure is defined as severe and irreversible kidney function impairment with an estimated glomerular filtration rate of < 15 mL/min/1.73 m² (GRF category G5)¹. Although hemodialysis has been an effectively and widely used treatment for kidney failure, it can often cause central nervous system complications, including cerebrovascular diseases², leukoencephalopathy³, and cognitive impairment⁴. These complications may lead to poor clinical outcomes, such as hospitalization and disability^{5,6}. Therefore, early diagnosis of central nervous system complications is vital to prevent the progression of these complications and provide the optimal treatment.

Recently MR techniques have played an important role in the early diagnosis of central nervous systems complications in hemodialysis patients. These techniques included resting-state functional MR imaging⁷, diffusion tensor imaging (DTI)⁸, arterial spin labeling (ASL)⁹, magnetic resonance spectroscopy (MRS)¹⁰, and susceptibility weighted imaging (SWI)¹¹. The application of these techniques has shown that there are abnormal brain changes in hemodialysis patients, such as impairments of functional connectivity¹², disruptions of white matter integrity⁸, cerebral blood flow changes⁹, abnormal brain metabolism¹⁰, and cerebral microbleeds¹¹. However, it has been reported that morphological changes can more directly reflect abnormal brain changes in hemodialysis patients¹³. To support this finding, brain atrophy has been assessed using predefined visual standards in hemodialysis patients¹⁴. However, this method was insensitive to microstructure changes and heavily depended on the experience levels of observers. Voxel-based morphometry (VBM) has been widely used to detect microstructure changes in patients with kidney failure¹⁵, hemodialysis^{16,17}, and chronic kidney disease (CKD)¹⁸. All of these studies found gray matter (GM) and white matter (WM) atrophy. However, most studies were cross-sectional, which was affected by the differences among the individuals and further caused the inaccuracies in the evaluation of cerebral volumes. To date, only Tsuruya et al.¹⁸ explored longitudinal brain volumes changes in CKD and peritoneal

dialysis patients and found that peritoneal dialysis patients had severe GM atrophy compared to CKD patients. It has also been reported that hemodialysis and peritoneal dialysis were different dialysis modalities and have different adverse effect on the cerebral structures¹⁹. However, few studies explored the effect of only regular hemodialysis therapy on the cerebral structures.

All these above VBM analyses were performed with the VBM8 toolbox implemented in Statistical Parametric Mapping 8 (SPM8) software. Recently, a new VBM toolbox called Computational Anatomy Toolbox (CAT) was introduced by a Structural Brain Mapping group (<http://www.neuro.uni-jena.de/cat/>). Compared to the previous VBM8 toolbox, the CAT12 toolbox is easier to operate because of increased automation, and more accurate and robust results²⁰. It has been reported that CAT12 has improved the normalization and segmentation during the VBM analysis²⁰. In recent years, the CAT12 toolbox had been widely used in brain volume analyses of diseases including Parkinson's disease²¹, Alzheimer's disease²², and depressive disorder²³. To date, there has been no studies to explore the longitudinal brain volumes changes in hemodialysis patients using the CAT12 toolbox.

We hypothesized that the process of hemodialysis may cause the aggravation of brain atrophy, which correlated with cognitive impairment. The purpose of this study was to investigate: 1) the brain volume changes in hemodialysis patients by cross-sectional and longitudinal MRI examinations using the CAT12 toolbox; 2) the clinical risk factors for the gray matter volume (GMV) changes; and 3) the correlations between brain volumes changes and cognitive function changes.

Methods

Subjects

This study was approved by the Medical Research Ethics Committee of our hospital (2015N002KY) and all the subjects offered their written informed consent form. A total of 97 hemodialysis patients were recruited from the Hemodialysis Center of the hospital from November 2015 to July 2019. The inclusion criteria were: 1) all the subjects were 18 years or older and right-handed; 2) all the patients completed the baseline and follow-up examinations to acquire all available MRI data; 3) the dialysis duration of patients was more than 3 months without history of peritoneal dialysis or kidney transplantation. The exclusion criteria included: 1) inability to complete the MRI examinations; 2) the subjects had other diseases affecting brain volumes including chronic infarction, hematoma, trauma, and some neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, etc.; 3) congenital brain abnormalities were found; 4) the image quality was too poor to perform VBM analysis. Based on the inclusion and exclusion criteria, 88 patients were enrolled (**Supplementary Fig. 1**). Each patient underwent the laboratory examination, neuropsychological and brain MRI assessment at baseline. The majority of them (50 of 88) received second examinations at follow-up. Finally, only 33 patients who met the inclusion and exclusion criteria were enrolled as follow-up group (1.75 ± 0.55 years) (**Supplementary Fig. 1**). All patients received regular hemodialysis therapy for four hours each time, three times a week. Seventy-six age-, sex-, and education-matched HCs were recruited from local communities in this city. HCs did not have the follow-up examinations.

Laboratory examinations and neuropsychological tests

To investigate the clinical risk factors for the brain volume changes in hemodialysis patients, blood biochemical examinations were performed within a week before MR scanning. The blood biochemical indices included

hemoglobin, serum urea, serum creatinine, serum phosphorus, calcium, and parathyroid hormone according to the previous studies and relative literatures^{24,25}. No blood biochemical tests were performed on HCs.

In order to assess cognitive function of all subjects, Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) tests were performed by a trained neuroradiologist (T.Z., who was trained by a 20 years' experienced neuropsychologist and blinded to the clinical information) in a quiet environment the day before MR scanning. The MMSE and MoCA tests were used to evaluate the cognitive function including orientation, registration, attention, calculation, recall, language and praxis. They had been widely applied in the cognitive evaluation of kidney failure and hemodialysis patients²⁶.

Imaging data acquisition and analysis

All MRI data were acquired on a 3 T MR imager (MAGNETOM Trio a Tim System, Siemens Healthcare) using an 8-channel phased-array head coil. All subjects were required to keep their head immobile during the MR examination. First, conventional MR sequences, including T₂WI and T₂ fluid attenuated inversion recovery (FLAIR) were applied to exclude the congenital cerebral abnormalities, occupying-space diseases, and demyelinating diseases. Then, high resolution 3D sagittal T₁-weighted images were obtained using magnetization-prepared rapid gradient-echo (MP-RAGE) sequence. The parameters of each sequences were presented in the **Supplemental Materials**.

The CAT12 Toolbox was used to perform VBM analyses within SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK) running on MATLAB (R2010b; MathWorks). For the patient's longitudinal data, we used longitudinal data segmentation to preprocess those images. The postprocessing steps of VBM analysis included the following steps: (1) All T₁ structure images were normalized and were bias-field corrected. (2) All images were aligned to Montreal Neurological Institute (MNI) standard space. (3) These images were segmented into white matter, GM, and cerebrospinal fluid. (4) After imaging segmentation, images of all subjects were checked to ensure to be further used for subsequent analysis. (5) A statistical analysis module was applied to estimate the total intracranial volume (TIV) of each subject. Finally, all data were smoothed on SPM12 with a kernel of 8 mm full width at half maximum (FWHM)²⁷. GMV was divided by TIV to acquire the normalized GMV in order to remove the effect of cerebral size variability.

Statistical Analyses

Statistical analyses were conducted using SPSS software (version 17.0, SPSS Inc.) and SPM12 package running on MATLAB (R2010b; MathWorks). First, the normal distribution of data was analyzed using the Kolmogorov–Smirnov test. The differences in age and education levels between hemodialysis patients and HCs were explored by Mann-Whitney U test. The differences in sex between hemodialysis patients and HCs were explored by Chi-square test. Two independent sample t test was employed to explore the differences in normalized GMV between patients and HCs at baseline. Paired-sample t test was conducted to evaluated the differences in normalized GMV between patients at baseline and follow-up. The differences in MMSE and MoCA scores between patients and HCs were investigated using the Mann-Whitney U test. Because the majority of patients refused to undergo second MoCA tests (28/33 at follow-up group) due to the long time of neuropsychological tests, the differences of MoCA scores between baseline and follow-up group were not analyzed in this study. The differences in MMSE scores between patients at baseline and follow-up were investigated using the Wilcoxon signed-rank test.

The clinical risk factors for brain volume changes in hemodialysis patients were investigated by stepwise multiple regression analysis. The correlations between brain volumes changes and MMSE scores changes in patients were

investigated using Spearman's correlation analysis. An FDR corrected $P < 0.05$ for stepwise multiple regression analysis was considered as significant.

Statistical analyses of structural MRI data were carried out using SPM12. The differences in GMV between patients at baseline and HCs were explored using two independent sample t test (with age, sex, and TIV as covariates, voxel-wise threshold of $P < 0.001$, false discovery rate [FDR] corrected). The differences in GMV between baseline and follow-up examination in patients were investigated by paired-sample t test (with age and TIV as covariates, voxel-wise threshold of $P < 0.05$, FDR corrected).

Results

Patient Characteristics

The demographics and neuropsychological tests of the cross-sectional study were presented in Table 1. There were no significant differences in age, sex, and education levels between patients and HCs ($P = 0.627$; 0.162 ; 0.875). The mean follow-up interval time was 1.75 ± 0.55 years. The MMSE scores of patients (27[26, 29]) were significantly lower than HCs (30[29, 30]) ($P < 0.001$). The MoCA scores of patients (22[19.48, 24.04]) were significantly lower than HCs (28[26.89, 29]) ($P < 0.001$). The MMSE scores of hemodialysis patients at follow-up (26[25, 28.5]) were significantly lower than those of patients at baseline (28[25, 29.5]) ($P = 0.02$). The characteristics, neuropsychological tests, and laboratory examinations of the longitudinal study were shown in Table 2. Compared to patients at baseline, patients at follow-up had significantly higher parathyroid hormone levels ($P = 0.026$).

Table 1
Demographics and neuropsychological tests in the cross-sectional study

	HCs	patients	<i>P</i>
Age(years)	46.5(35, 53.75)	47.5(33.25, 57)	0.627
Sex (M/F)	34/42	49/39	0.162
Education level	14(11, 15)	14(11, 15)	0.875
MMSE	30(29, 30)	27(26, 29)	$< 0.001^a$
MoCA	28(26.89, 29)	22(19.48, 24.04)	$< 0.001^a$
Normalized GMV(%)	35.47 ± 1.50	34.14 ± 1.90	$< 0.001^b$
GMV	520.30 ± 64.87	507.28 ± 61.04	0.187
TIV	1464.40 ± 148.05	1483.88 ± 135.94	0.381
Data conforming to normal distribution are expressed by mean $\pm$ standard deviation; data consistent with skewed distributions are represented by medians (percentiles25th, percentiles75th).			
HCs = Healthy Controls, MMSE = Mini-mental State Examination, MoCA = Montreal Cognitive Assessment, GMV = Gray Matter Volume, TIV = Total Intracranial Volume			
^a Mann-Whitney U test			
^b Two independent sample t test			

Table 2
Characteristics, neuropsychological tests, and laboratory examinations in final included patients from the longitudinal study

	Baseline	Follow up	<i>P</i>
MMSE	28(25, 29.5)	26(25, 28.5)	0.02 ^a
Normalized GMV(%)	33.92 ± 2.23	33.29 ± 2.4	0.001 ^b
Urea	27.71 ± 9.10	24.38 ± 8.58	0.063
Creatinine	953.4 ± 309.08	815.04 ± 417.94	0.087
Serum phosphorus	1.97 ± 0.54	1.80 ± 0.65	0.153
Parathyroid hormone	130.2(64.46, 226.3)	213.1(116.5, 408)	0.026 ^a
Hemoglobin	113.56 ± 3.16	115.94 ± 2.96	0.53
Data conforming to normal distribution are expressed by mean ± standard deviation; data consistent with skewed distributions are represented by medians (percentiles25th, percentiles75th).			
MMSE = Mini-mental State Examination, GMV = Gray Matter Volume			
^a Wilcoxon signed ranks test			
^b Paired samples test			

Brain volume changes between patients at baseline and HCs

The normalized GMV (%) of patients (34.14 ± 1.9) were significantly lower than that of HCs (35.47 ± 1.5) ($P=0.001$) (**Supplementary Fig. 2**). Compared to HCs, patients showed diffusely decreased GMV in the bilateral frontal lobes, temporal lobes, occipital lobe, parietal lobe, limbic system, caudate, putamen, and globus pallidus (FDR corrected with age, sex, and TIV as covariates; voxel-wise threshold of $P < 0.001$) (Fig. 1; **Supplementary Table 1**).

Brain volume changes between baseline and follow-up

The normalized GMV (%) of patients at baseline (33.92 ± 2.23) were significantly lower than that of patients at follow-up (33.29 ± 2.4) ($P = 0.001$) (**Supplementary Fig. 2**). Compared with patients at baseline, the patients at follow-up showed significantly decreased GMV in the bilateral frontal lobes, temporal lobes, insula, Rolandic operculum, caudate, right supplementary motor area, right precentral gyrus, right supramarginal gyrus, and right cingulate gyrus (with age and TIV as covariates, voxel-wise threshold of $P < 0.05$, FDR corrected) (Fig. 2; **Supplementary Table 1**).

Clinical risk factors for brain volume changes in hemodialysis patients

The independent risk factors for regional GMV changes included long hemodialysis duration, increased serum urea, and increased parathyroid hormone (Table 3). The Variance Inflation Factor (VIF) ranged from 1.000 to 1.008, indicating that there was no multicollinearity among the independent variables ²⁶.

Table 3

Independent risk factors for brain volume changes in hemodialysis patients using stepwise multiple regression analysis

Regional brain volume changes (AAL)	Blood biochemical factors	Standardized coefficients	95% Confidence interval	Partial correlation	Collinearity statistics VIF	P_{FDR}
Δ Insula_L	Urea	0.375	(0.000, 0.001)	0.375	1.000	0.046
Δ Rolandic_Oper_L	Urea	0.453	(0.000, 0.002)	0.453	1.000	0.030
Δ Frontal_Sup_Medial_L	Urea	0.327	(0.000, 0.000)	0.363	1.008	0.046
	parathyroid hormone	0.410	(0.000,0.001)	0.438	1.008	0.030
Δ Supp_Motor_Area_R	Urea	0.384	(0.000, 0.001)	0.348	1.000	0.045
Δ Frontal_Sup_Medial_R	parathyroid hormone	0.483	(0.000, 0.000)	0.512	1.008	0.020
	Urea	0.343	(0.000, 0.001)	0.398	1.008	0.045
Δ Cingulum_Mid_R	parathyroid hormone	0.445	(0.000,0.000)	0.445	1.000	0.030
Δ Temporal_Sup_R	duration	0.364	(0.000, 0.001)	0.364	1.000	0.046
AAL = Anatomical Automatic Labeling; GM = Gray Matter Volume; WM = White Matter Volume; VIF = Variance Inflation Factor						

Correlations between MMSE scores changes and brain volume changes

There was a significant positive correlation between the GMV changes of left caudate nucleus and the MMSE scores changes in hemodialysis patients using Spearman's correlation analysis ($r_s=0.437$, $P=0.033$) (Fig. 3).

Discussion

There were three vital findings in our study. First, compared with HCs, GMV in hemodialysis patients were diffusely decreased. Some regional GMV in hemodialysis patients at follow-up were also decreased compared to those patients at baseline. These findings indicate that hemodialysis patients suffered from brain atrophy over time. Second, the MMSE and MoCA scores of hemodialysis patients significantly lower than those in HCs. The MMSE scores in patients at follow-up were also significantly lower than those in patients at baseline. Furthermore, decreased GMV of left caudate nucleus showed significant positive correlation with reduced MMSE scores for the interval time between baseline and follow-up examinations, indicating that brain atrophy was associated with neurocognitive impairment. Third, long hemodialysis duration, increased serum urea, and increased parathyroid

hormone were independent risk factors for regional GMV changes in hemodialysis patients by longitudinal analysis.

Our study found diffusely decreased GMV in hemodialysis patients compared with HCs, furthermore, decreased GMV in patients at follow-up compared with patients at baseline. These findings suggested that hemodialysis patients are more likely to suffer from GM atrophy over time. In our study, age, sex, and TIV of all subjects were taken as covariates to exclude the effects of these factors. The reasons for GM atrophy may be: First, hemodialysis patients are more likely to suffer from cerebrovascular diseases²⁸ due to anemia²⁹, oxidative stress³⁰, and inflammation³⁰. Cerebrovascular diseases have been reported as one of the factors to affect regional brain volumes. The occurrence of cerebrovascular diseases results in ischemia and hypoxia of regional brain tissues, which could further lead to brain tissue damage and showed the brain atrophy³¹. In our study, we found that the more increased parathyroid hormone, the more increased GM atrophy, which supported this reason. The increased parathyroid hormone can cause the secondary hyperparathyroidism and cause the metabolic disorder of calcium and phosphorus. These further increase the cerebrovascular diseases risk²⁸. Second, renal failure leads to abnormal accumulation of organic toxic substances, such as urea, uric acid, guanidine compounds, and creatinine³². Some studies have found that creatinine and guanidine compounds existed in the cerebrospinal fluid of uremia patients^{29,33}. These neurotoxic substances may cause atrophy or death of glial cells and neurons, which further induce brain atrophy¹⁵. Our study also found that elevated serum urea can cause more decreased GM volumes, also supporting this finding. Third, a previous study had shown that iron deposition occurred in some brain regions of hemodialysis patients²⁴, which can cause oxidative stress, further damage brain tissues and cause brain atrophy¹⁷. Fourth, we found that follow-up duration was a risk factor for regional GMV decrease in hemodialysis patients. Patients were prone to cerebral ischemic vascular diseases due to the hemodynamic instability and decreased vascular autoregulation during the hemodialysis session³⁴.

Our findings of decreased regional GMV in hemodialysis patients were partially consistent with some cross-sectional studies^{15,16}. However, there were still a few differences between our study and other studies^{15,16}. In Zhang et al.'s study, they also found increased GMV of kidney failure patients mainly located in right extra-nuclear, right caudate, and right thalamus¹⁵. Gong et al.³⁵ revealed increased regional GMV of hemodialysis patients in bilateral thalamus¹⁶, and bilateral caudate³⁵. There are several possible explanations for these different findings: First, in the Gong et al.'s study³⁵, all the hemodialysis patients were diagnosed with secondary hyperparathyroidism, However, the patients in our study were just hemodialysis patients. Although they had the increased parathyroid hormone levels, they cannot diagnose as the secondary hyperparathyroidism due to the clinical diagnostic criteria. Second, some studies have also suggested that different dialysis modalities have different effects on the incidence and degrees of cerebrovascular diseases, which may also cause different degrees of brain atrophy³⁶. The study by Zhang et al.¹⁵ included both hemodialysis and peritoneal dialysis patients. However, the patients in our study were all hemodialysis patients. The comparison of effects of different dialysis modalities on the brain atrophy will need further investigation in the future.

We found that MMSE scores of patients at follow-up were significantly lower compared with patients at baseline, and the volumes changes of left caudate nucleus between two examinations were positively correlated with MMSE scores changes, indicating that brain atrophy was associated with the progressive neurocognitive impairment as the result of hemodialysis therapy. The caudate nucleus is an important part of frontostriatal brain circuit and it plays a role in cognitive function, especially executive function³⁷. Some studies had found that caudate nucleus

with discrete lesions caused executive function isolated deficits³⁸. Some studies also demonstrated that the caudate nucleus was involved in complicated processes such as complex sentences and ambiguity resolution³⁹. The MMSE test contained the high proportion of language test items, so it can correctly reflect the cognitive-related impairment caused by the decreased GMV of left caudate nucleus.

There were some limitations in our study. First, although our study explored longitudinal changes in brain volumes of hemodialysis patients, the HCs did not have follow-up examinations. The purpose of our study to observe the longitudinal changes of brain volumes in hemodialysis patients over time, so we mainly compared the brain volumes changes between patients at follow-up and baseline, between patients at baseline and HCs in our study. In order to avoid the effect of follow-up interval time on brain volumes, we also considered age, sex and TIV as covariates in the analysis. Second, the sample size of longitudinal study was relatively small, and a larger sample size is needed to explore the longitudinal brain volumes changes in hemodialysis patients. Third, our longitudinal study only relied on MMSE test, which may be not sensitive enough to mild cognitive impairment. MMSE also has some advantages including low false negative rate, short time consumption and simple operation in evaluation of moderate to severe cognitive impairment. It has been reported that the prevalence of mild to moderate cognitive impairment, severe impairment in patients were about 50% and 37%⁴⁰. Besides, the MMSE had also been applied in some longitudinal studies to evaluate the cognitive function of some other diseases⁴¹. In the future, we will add other neuropsychological tests to evaluate cognitive function of patients.

Conclusion

Our cross-section and longitudinal study indicated that hemodialysis patients suffered from diffused GM atrophy over time, which correlated with cognitive impairment. Hemodialysis duration, altered levels of serum urea, and parathyroid hormone were independent risk factors for regional brain atrophy.

Declarations

Acknowledgments

We would like to express our gratitude to Professor E. Mark Haacke from Wayne State University who helped us with the spell, grammar, and the structures of manuscript.

Declarations

Ethical Approval

This study was approved by the Medical Research Ethics Committee of our hospital (2015N002KY).

Consent to Participate

All the subjects offered their written informed consent form.

Consent to Publish

All the authors agreed to publish this article.

Authors Contributions

Huiying Wang and Lixiang Huang substantial contributed to conception and design, acquisition of data, or analysis and interpretation of data; performing statistical analyses; drafting the article or revising it critically for important intellectual content. Gemuer Wu contributed to conception and design; evaluation and acquisition of data. Jinping Li, Lei Liu, Tong Zhang, Jinxia Zhu, Xianchang Zhang, and Wen Shen contributions to conception and design. Chao Chai and Shuang xia contributed to conception and design; drafting the article or revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Huiying Wang and Lixiang Huang participated to an equal extent in planning, analyzing, evaluating, and writing the paper.

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Funding

This study has received funding by the Natural Scientific Foundation of China (grant number 81901728 to Chao Chai grant number 81501457 to Shuang Xia grant number 81873888 to Wen Shen), the National Key Technologies Research and Development Program of China (2019YFC0120901 to Shuang Xia), the Science and Technology talent cultivation Project of Tianjin Health Commission (grant number RC20185 to Chao Chai).

Competing Interests

The authors have no conflicts of interest to declare.

Availability of data and materials

A total of 97 hemodialysis patients were recruited from the Hemodialysis Center of our hospital from November 2015 to July 2019. Seventy-six age-, sex-, and education-matched HCs were recruited from local communities. The blood biochemical examinations were performed using a Vitros 350 Automatic Biochemical Analyzer (Johnson & Johnson, Warren, NJ) within a week before MR scanning. All MRI data were acquired on a 3 T MR imager (MAGNETOM Trio a Tim System, Siemens Healthcare) using an 8-channel phased-array head coil.

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Figures

Figure 1

Brain regions with significantly decreased gray matter volume between hemodialysis patients and HCs Compared to HCs, hemodialysis patients showed significantly decreased GMV in bilateral frontal lobes, temporal lobes, occipital lobe, parietal lobe, limbic system, caudate, putamen, and globus pallidus (FDR corrected with age, sex, and TIV as covariates; voxel-wise threshold of $P < 0.001$)

Figure 2

Brain regions with significantly decreased gray matter volume between baseline and follow-up patients Compared to patients at baseline, patients at follow-up showed significantly decreased GMV in the bilateral frontal lobes, temporal lobes, insula, Rolandic operculum, caudate, right supplementary motor area, right precentral gyrus, right supramarginal gyrus, and right cingulate gyrus (with age and TIV as covariates, voxel-wise threshold of $P < 0.05$, FDR corrected)

Figure 3

Correlation between changes of left caudate volume and changes of MMSE score The changes in the GM volume of left caudate nucleus between baseline and follow-up examinations were positively correlated with the changes of MMSE score ($r_s=0.437$, $P=0.033$)

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