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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Abstract
This study aimed to explore gray matter volume (GMV) changes in patients undergoing hemodialysis and assess the clinical risk factors associated with GMV changes and neuropsychologic test results. Eighty-eight hemodialysis patients and 76 healthy controls (HCs) were recruited in this study. Fifty patients underwent follow-up examinations (follow-up duration: 1.75 ± 0.55 years), including magnetic resonance imaging, blood biochemical, and neuropsychologic testing. Changes in GMV between the patients and HCs were assessed. Longitudinal GMV changes were also explored in the patients. The clinical risk factors associated with longitudinal GMV changes and the correlations between longitudinal GMV changes and neuropsychologic test results were analyzed in the patients. Patients undergoing hemodialysis had diffusely decreased GMV compared with HCs (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 concentrations, parathyroid hormone levels, and hemodialysis duration were independent risk factors for decreased GMV in patients undergoing hemodialysis (all \( P < 0.05 \), FDR corrected). Patients undergoing hemodialysis had lower mini-mental state examination (MMSE) (27[26, 29]) and Montreal cognitive assessment (MoCA) (22[19.5, 24.0]) scores than those of the HCs (30[29, 30] and 28[26.9, 29]) (all \( P < 0.05 \)). The MMSE scores of the 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 (\( r_s = 0.437, P = 0.033 \)). Patients undergoing hemodialysis had noticeable GM atrophy over time, related to cognitive impairments.

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

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Introduction

Central nervous system complications are common in patients undergoing hemodialysis (Viggiano et al., 2020) and include cerebrovascular diseases (Ghoshal & Freedman, 2019), leukoencephalopathy (Findlay et al., 2019), and cognitive impairment (Freire et al., 2020). These complications could lead to poor clinical outcomes, such as hospitalization and cognitive disabilities (Alqahtani et al., 2018; McQuillan & Jassal, 2010). Therefore, the early diagnosis of central nervous system complications is vital in preventing the progression of these complications and providing optimal therapeutic strategies.

Recently MR techniques have played an important role in the early diagnosis of central nervous systems complications in patients undergoing hemodialysis. These techniques include resting-state functional MR imaging (Jin et al., 2020a), diffusion tensor imaging (DTI) (Chou et al., 2019), arterial spin labeling (ASL) (Chai et al., 2020a), magnetic resonance spectroscopy (MRS) (Ma et al., 2018), and susceptibility weighted imaging (SWI) (Chai et al., 2016). With these techniques, abnormal brain changes, such as functional connectivity impairments (Wu et al., 2020), white matter integrity disruptions (Chou et al., 2019), cerebral blood flow changes (Chai et al., 2020a), abnormal brain metabolism (Ma et al., 2018), and cerebral microbleeds (Chai et al., 2016) have been demonstrated in patients undergoing hemodialysis. However, morphologic changes have been shown to more directly reflect abnormal brain changes in patients undergoing hemodialysis (Prohovnik et al., 2007). To support this finding, brain atrophy was assessed using predefined visual standards in patients undergoing hemodialysis (Drew et al., 2013). However, microstructural changes could not be detected with the methodology used and depended heavily on observer experience. Voxel-based morphometry (VBM) has been widely used to detect microstructural changes in patients with kidney failure (Drew et al., 2013), hemodialysis (Jin et al., 2020b; Chai et al., 2015), and chronic kidney disease (CKD) (Tsuruya et al., 2015). All of these studies found gray matter (GM) and white matter (WM) atrophy. However, most studies were cross-sectional design, which was affected by individual differences, causing further inaccuracies in cerebral volume determinations. To date, only Tsuruya et al. (Tsuruya et al., 2015) has explored longitudinal brain volume changes in patients with CKD and those undergoing peritoneal dialysis. In that study, patients undergoing peritoneal dialysis had more severe GM atrophy than patients with CKD. Hemodialysis and peritoneal dialysis have been reported to be different dialysis modalities with different adverse effects on cerebral structures (Lu et al., 2015). However, few studies have explored the effect of solely hemodialysis therapy on the cerebral structures.

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/). The CAT12 toolbox is easier to operate because of increased automation, and more accurate and robust results (Farokhian et al., 2017). It has been reported that CAT12 has improved the normalization and segmentation during the VBM analysis (Farokhian et al., 2017). In recent years, the CAT12 toolbox has been widely used to analyze brain volume in various diseases, including Parkinson’s disease (Kubera et al., 2019), Alzheimer’s disease (Seiger et al., 2018), and depressive disorders (Schmitgen et al., 2019). To date, there are no studies that have explored the changes in longitudinal brain volumes in patients undergoing hemodialysis using the CAT12 toolbox.

We hypothesized that the hemodialysis process would aggravate brain atrophy and that this aggravation would be correlated with cognitive impairments. The study aimed to investigate: 1) brain volume changes in patients undergoing hemodialysis using both cross-sectional and longitudinal MRI examinations with the CAT12 toolbox; 2) clinical risk factors associated with gray matter volume (GMV) changes; and 3) correlations between brain volume changes and functional cognitive impairments.

Methods

Subjects

This study was approved by the Medical Research Ethics Committee of our hospital (2015N002KY), and all the subjects signed written informed consents. 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 subjects were >18 years old and right-handed, 2) all patients completed the MRI examinations and all available data were acquired, 3) the duration of dialysis for all patients was > 3 months with no history of peritoneal dialysis or kidney transplantation. The exclusion criteria included 1) an inability to complete the MRI examinations; 2) the presence of other diseases affecting brain volumes, including chronic infarction, hematoma, trauma, and some neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease; 3) the presence of congenital brain abnormalities; 4) image quality too poor for the VBM analysis. Based on the inclusion and exclusion criteria, 88 patients were enrolled (the reasons for the exclusion of 9 patients are shown in Fig. 1). Each patient underwent laboratory examinations, neuropsychologic and brain MRI assessments at baseline. The majority of the
patients (50) received a second examination at follow-up. Of the 50 patients, 17 were excluded at follow-up because of poor image quality (6), cerebral hemorrhage lesions (4), chronic infarction lesions (2), and incomplete examinations due to malaise (5). Finally, 33 patients were enrolled in the follow-up group (Fig. 1). The follow-up duration was 1.75 ± 0.55 years. All patients received regular 4-hour hemodialysis therapy 3 times per week. Seventy-six age-, sex-, and education-matched HCs were recruited from local communities in our city. HCs did not have follow-up examinations.

To assess cognitive function in 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 neuropsychologist with 20 years of experience and blinded to the clinical information) in a quiet environment one day before MR scanning. The MMSE and MoCA tests were used to evaluate cognitive function, including orientation, registration, attention, calculation, recall, language, and praxis. These tests have been widely used for cognitive evaluations of patients with kidney failure and those undergoing hemodialysis (Chai et al., 2019).

Imaging data acquisition and analysis

All MRI data were acquired on a 3 T MR system (MAGNETOM Trio a Tim System, Siemens Healthcare, Erlangen, Germany) using a 8-channel phased-array head coil. All subjects were required to keep their head immobile during the MR examination. First, conventional MR sequences, including T1WI and T2 fluid-attenuated inversion recovery (FLAIR) were applied to exclude congenital cerebral abnormalities, space-occupying diseases, and demyelinating diseases. Then, high-resolution 3D sagittal T1-weighted images were obtained using a magnetization-prepared rapid gradient-echo (MP-RAGE) sequence. The parameters of each sequence are presented in the Supplementary Materials.
The CAT12 Toolbox was used to perform VBM analyses within SPM12 software (Statistical Parametric Mapping, Institute of Neurology, London, UK) performed on the MATLAB platform (R2010b; MathWorks). For the patient’s longitudinal data, we used longitudinal data segmentation to preprocess the images. The VBM analysis postprocessing steps included the following (1) All T1 structure images were normalized and were bias-field corrected, (2) All images were aligned to the Montreal Neurological Institute (MNI) standard space, (3) All images were segmented into white matter, GM, and cerebrospinal fluid, (4) After imaging segmentation, all images were checked to ensure they could be used for subsequent analyses, (5) A statistical analysis module was applied to estimate the total intracranial volume (TIV) of each subject, and (6) all data were smoothed with the SPM12 software package and an 8 mm full-width at half maximum (FWHM) kernel (Chai et al., 2020b). GMV were normalized and were bias-field corrected, (2) All images were aligned to the Montreal Neurological Institute (MNI) standard space, (3) All images were segmented into white matter, GM, and cerebrospinal fluid, (4) After imaging segmentation, all images were checked to ensure they could be used for subsequent analyses, (5) A statistical analysis module was applied to estimate the total intracranial volume (TIV) of each subject, and (6) all data were smoothed with the SPM12 software package and an 8 mm full-width at half maximum (FWHM) kernel (Chai et al., 2020b). GMV were divided by TIV to acquire normalized GMV to remove the effect of cerebral size variability.

Statistical Analyses

Statistical analyses were conducted using SPSS software (version 17.0, SPSS Inc.) and the SPM12 package performed on the MATLAB platform. First, data were analyzed for normal distributions using the Kolmogorov–Smirnov test. The differences in age and education levels between patients undergoing hemodialysis and HCs were explored using the Mann-Whitney U test. Sex differences between hemodialysis patients and HCs were explored using the Chi-square test. An independent samples t-test was employed to explore the differences in normalized GMV between patients undergoing hemodialysis and HCs at baseline. A paired-samples t-test was conducted to evaluate the differences in normalized GMV between the patients at baseline and follow-up. The differences in MMSE and MoCA scores between patients at baseline and the HCs were investigated using the Mann-Whitney U test. Because the majority of patients (28) refused to undergo second MoCA tests due to the relative long examination time (more than or about 20 minutes) of MMSE and MoCA tests together (other reasons listed in the limitations), 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 the brain volume changes in patients undergoing hemodialysis were investigated using stepwise multiple regression analysis. The correlations between brain volume and MMSE score changes were investigated using the Spearman’s correlation analysis. An FDR corrected \( P < 0.05 \) for the stepwise multiple regression analysis was considered significant.

Statistical analyses of the structural MRI data were carried out using the SPM12 package. The differences in GMV between patients at baseline and HCs were explored using an independent samples 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 the baseline and follow-up examinations in patients undergoing hemodialysis were investigated with the paired-samples t-test (with age and TIV as covariates, and a voxel-wise threshold of \( P < 0.05 \), FDR corrected). The GM probability mask was used to include the voxels with a value >0.3 in the CAT12 Dartel GM template (Lin et al., 2020).

Results

Patient Characteristics

The demographics and neuropsychologic tests of the cross-sectional study are presented in Table 1. There were no significant differences in age, sex, and education levels between the patients and HCs (\( P = 0.627; 0.162; 0.875 \)). The mean follow-up duration was 1.75 ± 0.55 years. The MMSE scores of patients (27[26, 29]) were significantly lower than those of the HCs (30[29, 30]) (\( P < 0.001 \)). The MoCA scores of patients (22[19.5, 24.0]) were significantly lower than those of the HCs (28[26, 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, neuropsychologic tests, and laboratory examinations of the longitudinal study are shown in Table 2.

| Table 1. Demographics and neuropsychologic tests in the cross-sectional study |
|---------------------------------|---------|--------|-----|
| Age               | 46.5(35, 53.75) | 47.5(33.25, 57) | 0.627 |
| Sex       | 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 (mm³) | 520.30±64.87 | 507.28±61.04 | 0.187 |
| TIV (mm³) | 1464.40±148.05 | 1483.88±135.94 | 0.381 |

Data conforming to normal distribution are expressed by mean±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

^aMann-Whitney U test

^bTwo independent sample t test
The only significant difference noted was significantly higher parathyroid hormone levels in patients at follow-up compared with those at baseline ($P=0.026$).

**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 Figure 1). Compared with 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; a voxel-wise threshold of $P<0.001$) (Fig. 2A; Supplementary Table 1).

**Brain volume changes between baseline and follow-up**

The normalized GMV (%) of patients at follow-up (33.29±2.4, %) were significantly lower than that of patients at baseline (33.92±2.23, %) ($P=0.001$) (Supplementary Figure 1). 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. 2B; Supplementary Table 1).

**Clinical risk factors for brain volume changes in patients undergoing hemodialysis**

The independent risk factors for regional GMV changes included long hemodialysis durations, increased serum urea concentrations, and high parathyroid hormone concentrations (Table 3). The Variance Inflation Factor (VIF) ranged from 1.000 to 1.008, indicating that no multicollinearity was present among the independent variables (Chai et al., 2019).

**Correlations between MMSE scores changes and brain volume changes**

There was a significant positive correlation between GMV changes of the left caudate nucleus and 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 this study. First, GMV were decreased in patients at follow-up compared with patients at baseline, indicating that patients undergoing hemodialysis suffer from brain atrophy over time. This is the first longitudinal study to explore brain volume changes of patients undergoing hemodialysis over time. Second, the MMSE and MoCA scores of hemodialysis patients were significantly lower than those of the HCs. The MMSE scores in...
patients at follow-up were also significantly lower than those in patients at baseline. Furthermore, decreased GMV of the left caudate nucleus showed a 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 over time. Third, the longitudinal analysis showed that long hemodialysis durations, increased serum urea, and high parathyroid hormone level were independent risk factors for regional GMV changes in patients undergoing hemodialysis.

Our study found decreased GMV in patients at follow-up compared with patients at baseline, suggesting that hemodialysis patients are more likely to suffer from GM atrophy over time. In our study, the age, sex, and TIV of all subjects were taken as covariates to exclude the effects of these factors. The reasons for GM atrophy could have been due to several causes. First, patients undergoing hemodialysis are more likely to suffer from cerebrovascular diseases (Ediri Arachchi et al., 2020) due to anemia (Kelly & Rothwell, 2020), oxidative stress (Brancaccio et al., 2004), and inflammation (Brancaccio et al., 2004). Cerebrovascular disease has been reported to be a factor that affects regional brain volumes. Cerebrovascular diseases result in ischemia and hypoxia of regional brain tissues, which could lead to further brain tissue damage and brain atrophy (Rapa et al., 2019). In our study, we found that as parathyroid hormone...
concentrations increased, GM atrophy increased, supporting the findings of the previous study. Increased parathyroid hormone levels can cause secondary hyperparathyroidism, resulting in calcium and phosphorus metabolic disorders, which further increase cerebrovascular disease risk (Ediri Arachchi et al., 2020). Second, renal failure leads to an abnormal accumulation of organic toxic substances, such as urea, uric acid, guanidine compounds, and creatinine (Pedraza et al., 2020). Some studies have found that creatinine and guanidine compounds are present in the cerebrospinal fluid of patients with uremia (Kelly & Rothwell, 2020; Marini et al., 2020). These neurotoxic substances can cause atrophy or death of glial cells and neurons, further inducing brain atrophy (Zhang et al., 2013). Our study also found that elevated serum urea concentrations are associated with greater decreases in GMV, which is in support of those previous findings. Third, a previous study has shown that iron deposition occurred in some brain regions of patients undergoing hemodialysis (De Deyn et al., 2009). Iron deposition has been shown to cause oxidative stress, damaging brain tissues and causing brain atrophy (Chai et al., 2015). Fourth, we found that the follow-up duration was a risk factor for regional GMV decreases in patients undergoing hemodialysis. In another study, patients undergoing hemodialysis were prone to ischemic cerebral vascular diseases due to hemodynamic instability and decreased vascular autoregulation during hemodialysis sessions (Wolfgram, 2019).

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 over time. The caudate nucleus is an

### Table 3. Independent risk factors for brain volume changes using stepwise multiple regression analysis in patients undergoing hemodialysis

| Regional brain volume changes (AAL) | Blood biochemical factors | Standardized coefficients | 95% Confidence interval | Partial correlation | Collinearity statistics | $P_{FDR}$ |
|-------------------------------------|---------------------------|---------------------------|-------------------------|---------------------|-------------------------|----------|
| Insula_L                            | Urea                      | 0.375                     | (0.000, 0.001)          | 0.375               | 1.000                   | 0.036    |
| Rolandic_Oper_L                     | Urea                      | 0.453                     | (0.000, 0.002)          | 0.453               | 1.000                   | 0.020    |
| Frontal_Sup_Medial_L                | Urea                      | 0.343                     | (0.000, 0.001)          | 0.342               | 1.008                   | 0.035    |
| Supp_Motor_Area_R                   | parathyroid hormone       | 0.482                     | (0.000, 0.000)          | 0.480               | 1.008                   | 0.009    |
| Frontal_Sup_Medial_R                | parathyroid hormone       | 0.483                     | (0.000, 0.001)          | 0.521               | 1.008                   | 0.009    |
| Cingulum_Mid_R                      | parathyroid hormone       | 0.445                     | (0.000, 0.000)          | 0.398               | 1.008                   | 0.035    |
| Temporal_Sup_R                      | duration                  | 0.364                     | (0.000, 0.001)          | 0.364               | 1.000                   | 0.038    |

**Note:**
- AAL = Anatomical Automatic Labeling; VIF = Variance Inflation Factor
- $P_{FDR}$: False Discovery Rate

![Fig. 3. Correlation between changes in the left caudate volume and the MMSE score. The changes in the gray matter volume (GMV) of the left caudate nucleus between baseline and follow-up examinations were positively correlated with mini-mental state examination (MMSE) score changes ($r_s=0.437$, $P=0.033$)](image-url)
important part of the frontostriatal brain circuit and plays a role in cognitive function, especially executive function (Jeon et al., 2014). Some studies have found that discrete lesions in the caudate nucleus caused isolated deficits in executive function (Postuma & Dagher, 2006). Another study also demonstrated that the caudate nucleus is involved in complicated processes, such as complex sentence formation and ambiguity resolution (Mestres-Misse et al., 2012). The MMSE test contained the highest proportion of language test items compared with other cognitive assessments; therefore, it can correctly reflect the cognitive-related impairment caused by the decreased GMV of the left caudate nucleus.

Our findings of decreased regional GMV in patients undergoing hemodialysis were partially consistent with a few previous cross-sectional studies (Zhang et al., 2013; Jin et al., 2020b). However, a few differences between our study and other studies were also found (Zhang et al., 2013; Jin et al., 2020b). Zhang et al. also found increased GMV in patients with renal failure, and these decreases were mainly located in the right extra-nuclear region, right caudate nucleus, and right thalamus (Zhang et al., 2013). Gong et al. (Gong et al., 2020) revealed increased regional GMV of the thalamus and bilateral caudate nucleus in patients undergoing hemodialysis. There are several possible explanations for these different findings. First, in the study by Gong et al. (Gong et al., 2020), all patients undergoing hemodialysis were diagnosed with secondary hyperparathyroidism. The patients in our study did not have secondary hyperparathyroidism, and although they had increased parathyroid hormone levels, they did not present with the clinical diagnostic criteria of secondary hyperparathyroidism. Second, some studies have also suggested that different dialysis modalities have differing effects on the incidence and degree of cerebrovascular disease, which might also cause different degrees of brain atrophy (Drew & Sarnak, 2014). The study by Zhang et al. (Zhang et al., 2013) included patients with both hemodialysis and peritoneal dialysis, whereas those of our study only underwent hemodialysis. Therefore, the comparison of how different dialysis modalities affect brain atrophy will need further investigations.

There were some limitations to our study. First, although our study explored longitudinal changes in brain volumes of patients undergoing hemodialysis, the HCs did not have follow-up examinations. The purpose of our study was to observe the longitudinal changes in the brain volumes of patients undergoing hemodialysis over time; thus, we mainly compared the brain volume changes between patients at follow-up and baseline and patients at baseline and HCs in our study. To avoid the effect of follow-up interval times on brain volumes, we also considered age, sex, and TIVs as covariates in the analysis. Second, the sample size of the longitudinal study was relatively small. Larger sample sizes will be needed to explore the longitudinal brain volumes changes in patients undergoing hemodialysis. Third, our longitudinal study only relied on the MMSE test because some patients refused to perform the MoCA test in the longitudinal study at follow-up. The reason for refusal is that some patients felt uncomfortable at the follow-up examinations due to fluctuations in water, electrolytes, and metabolites and wanted to finish the examinations as soon as possible after hemodialysis. Some thought that a few of the items in the MoCA test were repeated in the MMSE test, and some did not want to undergo the relatively long study procedure. The MMSE also has some advantages, including a low false-negative rate, short time consumption, and simple operation. Mild to moderate and severe cognitive impairments of approximately 50% and 37%, respectively, have been shown with MMSE testing in patients undergoing hemodialysis (Murray et al., 2006). In addition, the MMSE has already been widely applied in some cross-sectional and longitudinal studies to evaluate the cognitive function of other diseases (Fruehwirt et al., 2019).

Conclusions

Our cross-sectional and longitudinal study indicated that hemodialysis patients suffered from noticeable GM atrophy over time, which correlated with cognitive impairment. Extended hemodialysis durations, increased serum urea levels, and high parathyroid hormone concentrations were found to be independent risk factors for regional brain atrophy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11682-021-00602-9.

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Authors Contributions Huiying Wang contributed to the conception and design, data acquisition, and data analysis and interpretation, performed statistical analyses, drafted and revised the article to provide important intellectual content. Lixiang Huang and Gemuer Wu contributed to the study conception and design, data evaluation and acquisition. Jinping Li, Lei Liu, Tong Zhang, Jinxia Zhu, Xianchang Zhang, and Wen Shen contributed to the study conception and design. Chao Chai and Shuang Xia contributed to the study conception and design, drafted and revised the article to provide important intellectual content, and agreed to be accountable for all aspects of the work to ensure that questions on the accuracy or integrity of the work were appropriately investigated and resolved.

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Data Availability A total of 97 patients undergoing hemodialysis 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 the week before MR scanning. All MRI data were acquired on a 3 T MR system (MAGNETOM Trio a Tim System, Siemens Healthcare, Erlangen, Germany), using an 8-channel phased-array head coil.

Compliance with ethical standards

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

Consent to Participate All subjects provided a written informed consent form.

Consent to Publish All the authors agreed to publish this article.

Competing Interests The authors have no conflicts of interest to declare.

References

Alqahtani F, Berzinger CO, Aljohani S, et al. Temporal Trends in the Outcomes of Dialysis Patients Admitted With Acute Ischemic Stroke. J Am Heart Assoc 2018;7(12).

Brandcaccio, D., Cozzolino, M., & Gallieni, M. (2004). Hyperparathyroidism and anemia in uremic subjects: a combined therapeutic approach. J Am Soc Nephrol, 15, S21–S24.

Chai, C., Wang, H., Chu, Z., et al. (2020b). Reduced regional cerebral venous oxygen saturation is a risk factor for the cognitive impairment in hemodialysis patients: a quantitative susceptibility mapping study. Brain Imaging Behav, 14, 1339–1439.

Chai, C., Wang, H., Liu, S., et al. (2019). Increased iron deposition of deep cerebral gray matter structures in hemodialysis patients: A longitudinal study using quantitative susceptibility mapping. J Magn Reson Imaging, 49, 786–799.

Chai, C., Wang, Z., Fan, L., et al. (2016). Increased Number and Distribution of Cerebral Microbleeds Is a Risk Factor for Cognitive Dysfunction in Hemodialysis Patients: A Longitudinal Study. Medicine (Baltimore), 95, e2974.

Chai, C., Zhang, M., Long, M., et al. (2015). Increased brain iron deposition is a risk factor for brain atrophy in patients with haemodialysis: a combined study of quantitative susceptibility mapping and whole brain volume analysis. Metab Brain Dis, 30, 1009–1016.

Chai, C., Zhang, M., Wang, H., et al. (2020a). Increased cerebral blood flow is correlated with neurocognitive impairment in long-term hemodialysis patients: an arterial spin labeling MRI study. Brain Imaging Behav.

Chou, M. C., Ko, C. H., Chang, J. M., & Hsieh, T. J. (2019). Disruptions of brain structural network in end-stage renal disease patients with long-term hemodialysis and normal-appearing brain tissues. J Neurolourad, 46, 256–262.

De Deyn, P. P., Vanholder, R., Elloot, S., & Glorieux, G. (2009). Guanidino compounds as uremic (neuro)toxins. Semin Dial, 22, 340–345.

Drew, D. A., Bhadelia, R., Tighiouart, H., et al. (2013). Anatomic brain disease in hemodialysis patients: a cross-sectional study. Am J Kidney Dis, 61, 271–278.

Drew, D. A., & Sarnak, M. J. (2014). Ischemic and hemorrhagic stroke: high incidence in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis, 63, 547–548.

Ediri Arachchi, W., Peng, Y., Zhang, X., et al. (2020). A Systematic Characterization of Structural Brain Changes in Schizophrenia. Neurosci Bull, 36, 1107–1122.

Farokhian, F., Beheshti, I., Sone, D., & Matsuda, H. (2017). Comparing CAT12 and VBMS for Detecting Brain Morphological Abnormalities in Temporal Lobe Epilepsy. Front Neurol, 8, 428.

Findlay, M. D., Dawson, J., Dickie, D. A., et al. (2019). Investigating the Relationship between Cerebral Blood Flow and Cognitive Function in Hemodialysis Patients. J Am Soc Nephrol, 30, 147–158.

Freire, D. M. C., Diogenes, D. S. B., Costa, B. G., et al. (2020). Cognitive impairment, endothelial biomarkers and mortality in maintenance haemodialysis patients: a prospective cohort study. Nephrol Dial Transplant, 35, 1779–1785.

Fruehwirt, W., Dorffner, G., Roberts, S., et al. (2019). Associations of event-related brain potentials and Alzheimer’s disease severity: A longitudinal study. Prog Neuropsychopharmacol Biol Psychiatry, 92, 31–38.

Ghoshal, S., & Freedman, B. I. (2019). Mechanisms of Stroke in Patients with Chronic Kidney Disease. Am J Nephrol, 50, 229–239.

Gong, X., Zou, L., Wu, H., et al. (2020). Altered brain structural and cognitive impairment in end-stage renal disease patients with secondary hyperparathyroidism. Acta Radiol, 61, 796–803.

Jeon, H. A., Anwander, A., & Friederici, A. D. (2014). Functional network mirrored in the prefrontal cortex, caudate nucleus, and thalamus: high-resolution functional imaging and structural connectivity. J Neurosci, 34, 9202–9212.

Jiang, W., Hu, C. Y., Li, F. L., Hua, X. G., Huang, K., & Zhang, X. J. (2020). Elevated parathyroid hormone levels and cognitive function: A systematic review. Arch Gerontol Geriatr, 87, 103985.

Jin, M., Wang, L., Wang, H., et al. (2020a). Altered resting-state functional networks in patients with hemodialysis: a graph-theoretical based study. Brain Imaging Behav.

Jin, M., Wang, L., Wang, H., et al. (2020b). Structural and Functional Alterations in Hemodialysis Patients: A Voxel-Based Morphometry and Functional Connectivity Study. Front Hum Neurosci, 14, 80.

Kelly, D., & Rothwell, P. M. (2020). Disentangling the multiple links between renal dysfunction and cerebrovascular disease. J Neurol Neurosurg Psychiatry, 91, 88–97.

Kubera, K. M., Schmitgen, M. N., Nagel, S., et al. (2019). A search for cortical correlates of trait impulsivity in Parkinson’s disease. Behav Brain Res, 369, 111911.

Lin, C., Lin, H., Wang, S., & Fuh, J. (2020). Association between regional brain volume and masticatory performance differed in cognitively impaired and non-impaired older people. Exp Gerontol, 137, 110942.

Lu, R., Kiernan, M. C., Murray, A., Rosner, M. H., & Ronco, C. (2015). Kidney-brain crosstalk in the acute and chronic setting. Nat Rev Nephrol, 11, 707–719.

Ma, X., Zhang, Y., Ma, S., et al. (2018). Association between abnormal thalamic metabolites and sleep disturbance in patients with end-stage renal disease. Metab Brain Dis, 33, 1641–1648.

Marini, S., Georgakis, M. K., Chung, J., et al. (2020). Genetic overlap and causal inferences between kidney function and cerebrovascular disease. Neurology, 94, e2581–e2591.

McQuillan, R., & Jassal, S. V. (2010). Neuropsychiatric complications of chronic kidney disease. Nat Rev Nephrol, 6, 471–479.
Mestres-Misse, A., Turner, R., & Friederici, A. D. (2012). An anterior-posterior gradient of cognitive control within the dorsomedial striatum. *Neuroimage, 62*, 41–47.

Murray, A. M., Tupper, D. E., Knopman, D. S., et al. (2006). Cognitive impairment in hemodialysis patients is common. *Neurology, 67*, 216–223.

Pedraza, M. I., de Lera, M., Bos, D., et al. (2020). Brain Atrophy and the Risk of Futile Endovascular Reperfusion in Acute Ischemic Stroke. *Stroke, 51*, 1514–1521.

Postuma, R. B., & Dagher, A. (2006). Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. *Cereb Cortex, 16*, 1508–1521.

Prohovnik, I., Post, J., Uribarri, J., Lee, H., Sandu, O., & Langhoff, E. (2007). Cerebrovascular effects of hemodialysis in chronic kidney disease. *J Cereb Blood Flow Metab, 27*, 1861–1869.

Rapa SF, Di Iorio BR, Campiglia P, Heidland A, Marzocco S. Inflammation and Oxidative Stress in Chronic Kidney Disease-Potential Therapeutic Role of Minerals, Vitamins and Plant-Derived Metabolites. *Int J Mol Sci 2019;21(1).*

Schmitgen, M. M., Depping, M. S., Bach, C., et al. (2019). Aberrant cortical neurodevelopment in major depressive disorder. *J Affect Disord, 243*, 340–347.

Seiger, R., Ganger, S., Kranz, G. S., Hahn, A., & Lanzenberger, R. (2018). Cortical Thickness Estimations of FreeSurfer and the CAT12 Toolbox in Patients with Alzheimer’s Disease and Healthy Controls. *J Neuroimaging, 28*, 515–523.

Tsuruya, K., Yoshida, H., Kuroki, Y., et al. (2015). Brain atrophy in peritoneal dialysis and CKD stages 3-5: a cross-sectional and longitudinal study. *Am J Kidney Dis, 65*, 312–321.

Viggiano, D., Wagner, C. A., Martino, G., et al. (2020). Mechanisms of cognitive dysfunction in CKD. *Nature reviews. Nephrology, 16*, 452–469.

Wolfgram, D. F. (2019). Intradialytic Cerebral Hypoperfusion as Mechanism for Cognitive Impairment in Patients on Hemodialysis. *J Am Soc Nephrol, 30*, 2052–2058.

Wu, B., Li, X., Zhang, M., et al. (2020). Disrupted brain functional networks in patients with end-stage renal disease undergoing hemodialysis. *J Neurosci RES, 98*, 2566–2578.

Zhang, L. J., Wen, J., Ni, L., et al. (2013). Predominant gray matter volume loss in patients with end-stage renal disease: a voxel-based morphometry study. *Metab Brain Dis, 28*, 647–654.

Zheng, K., Qian, Y., Lin, T., et al. (2020). Carotid intima–media thickness relative to cognitive impairment in dialysis patients, and their relationship with brain volume and cerebral small vessel disease. *Ther Adv Chronic Dis, 11*, 254072217.

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