Mechanisms of Cognitive Impairment in Chronic Kidney Disease

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A notable feature of dementia in chronic kidney disease (CKD) patients is the high frequency of vascular dementia, making its prevention through the management of classical risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, etc., associated with atherosclerosis and arteriosclerosis. Other effective measures, including the use of renin–angiotensin system inhibitors, addressing anemia, exercise therapy, and lifestyle improvements, have been reported. The incidence and progression of cognitive impairment (CI) may also be influenced by the type of kidney replacement therapy, with reports suggesting that long-duration dialysis, low-temperature hemodialysis, peritoneal dialysis, and kidney transplantation can have a preferable effect on the preservation of cognitive function. In conclusion, patients with CKD are at a higher risk of developing CI, with brain atrophy being a contributing factor.

Keywords: brain atrophy ; cognitive impairment ; chronic kidney disease ; dialysis

1. Introduction

In Japan, which is rapidly moving towards a hyper-aged society, the number of patients with cognitive impairment (CI) is increasing rapidly, along with the number of those with chronic kidney disease (CKD) [1][2][3]. In recent years, it has become evident that CKD patients have a higher frequency of CI, and various studies have been conducted to explore the mechanisms, relationships, and strategies concerning CKD and CI [4][5][6][7][8]. Although many findings have been presented, numerous problems remain unresolved [9][10][11]. On the other hand, it has been shown that cerebral atrophy progresses rapidly in patients with CKD, especially in dialysis patients [12][13][14][15][16][17]. Brain atrophy is significantly associated with CI, and atrophy of the frontal lobe and hippocampus is more remarkable in such patients [13][18][19].

2. Brain Atrophy in Patients with CKD

2.1. Brain Atrophy in Patients with Non-Dialysis Dependent CKD (ND)

The brain volume in ND patients has been reported to exhibit more advanced brain atrophy compared to that in healthy controls [20][21][22]. Recently, the relationship between urinary protein and renal function levels and brain volume was examined by magnetic resonance imaging (MRI) in 8630 participants from the general population in Japan, and it was reported that the higher the urinary albumin excretion and the lower the estimated glomerular filtration rate (eGFR), the lower the whole brain volume and the faster the progression of brain atrophy [22]. In contrast, Grasing et al. [23] reported no significant association between brain volumes and the eGFR in a cross-sectional analysis of 1596 participants from the database of the Alzheimer's Disease Neuroimaging Initiative (ADNI) with a mild to moderately reduced eGFR, as revealed by a multiple linear regression model. While unadjusted associations were initially observed, these were later attributed to the confounding effect of age.

2.2. Brain Atrophy in Patients on Hemodialysis (HD)

Brain atrophy has been demonstrated in several reports [12][13][14][15][16][17]. Yoshimitsu et al. [24] evaluated brain atrophy in 55 HD patients and 35 healthy subjects using the ventricular–brain ratio (VBR) quantified from MRI images, and reported that the VBR of HD patients was significantly greater at every 10 years of age in the 30s to 60s age range. In HD patients, the frequency of brain atrophy is high even at a young age, and it is thought that the mechanism cannot be explained by aging alone.

2.3. Brain Atrophy in Patients on Peritoneal Dialysis (PD)

In recent years, it has been reported that the brain gray matter volume (GMV) and GMV ratio (GMR) decrease with age, but the white matter volume (WMV) and WMV ratio (WMR) remain unchanged, as revealed through the analysis of brain MRI using statistical parametric mapping (SPM) [25]. Subsequently, researchers conducted an analysis using SPM on brain MRI data from patients with ND, PD, and HD, comparing both brain volume and the rate of change [26][27].

2.3.1. Comparison between PD and ND Patients

It has been reported that cognitive function is more impaired in PD patients than in ND patients [28]. However, there have been few studies examining the brain volume in PD patients, and none specifically comparing them [29]. Therefore, researchers conducted a comparison of brain volume and its change over time between the two patient groups [26].

First, in a cross-sectional study involving 69 patients with ND (ages 61 ± 10 years, 37/32 males and females, eGFR 39 ± 12 mL/min/1.73 m^2) and 62 PD patients (ages 60 ± 12 years, 41/21 males and females), researchers observed a significant negative correlation between GMR and age, whereas WMR did not exhibit a correlation with age [26]. Moreover, the regression line was lower in PD patients compared to ND patients (indicating smaller GMR in PD patients at the same age), and this difference further increased with age [26].

In a subsequent longitudinal study involving 61 ND patients (age 61 ± 10 years, 32/29 males and females, eGFR 39 ± 12 mL/min/1.73 m^2) and 34 PD patients (age 60 ± 11 years, 21/13 males and females) who underwent brain MRI examinations after a 2-year interval, researchers found that the annual change in GMR (AC-GMR) was −0.38 ± 0.10 percentage-points/year in ND patients and −0.83 ± 0.14 percentage points/year in PD patients. This indicates that brain atrophy progressed more than two times faster in PD patients compared to ND patients [26]. According to a report on general healthy subjects, GMR decreases with age at a rate of 0.2–0.3 percentage points/year, suggesting that brain atrophy progresses three times more rapidly in PD patients than in healthy subjects.

2.3.2. Comparison between PD and HD Patients

Next, researchers conducted a comparison of brain atrophy between PD and HD patients. In total, 73 PD and 34 HD patients who underwent brain MRI were recruited for a cross-sectional analysis. Among them, 42 PD and 25 HD patients who underwent a second brain MRI after 2 years were recruited for a longitudinal analysis. In the cross-sectional analysis, GMR was significantly lower in PD patients than in HD patients [least square mean (LSM): 39.2% vs. 40.0%, $p = 0.018$). AC-GMR was significantly greater in PD patients than in HD patients, and this difference remained statistically significant even after adjusting for potential confounding factors (LSM: −0.68 vs. −0.28 percentage-points/year, $p = 0.011$) [5].

3. Relationship between Brain Atrophy and CI in CKD Patients

The association between brain volume, brain atrophy, and cognitive function has been extensively investigated in studies involving Parkinson's disease, multiple sclerosis, Alzheimer's disease, and the general population; yet, few studies have explored the relationship between CI and white matter lesions, as well as brain atrophy, in CKD patients [28][30][31][32][33]. Yeh et al. [34] found a significant correlation between attention and executive function and white matter lesions, but no correlation with brain atrophy.

Researchers conducted a trail making test (TMT) in 95 ND patients who underwent MRI and examined the relationship between TMT scores and brain volume. Researchers demonstrated a significant negative correlation between TMT scores and GMR, and this significance persisted even after adjusting for confounding factors such as age, sex, diabetes mellitus, eGFR, educational history, systolic blood pressure, smoking and alcohol consumption, hemoglobin level, history of cardiovascular disease, and amount of urinary protein [6].

More interestingly, when the brain was partitioned into four regions (frontal lobe, temporal lobe, parietal lobe, and occipital lobe), and the correlation between the GMR and TMT scores in each region was investigated, a significant negative correlation was observed in the frontal and temporal lobes even after adjusting for multivariable variables. No correlation was found in the parietal and occipital lobes. This suggests that the atrophy of the frontal and temporal lobes contributes to the decline in frontal lobe function (executive function).

4. Mechanisms of CI in Chronic Kidney Disease

4.1. Atherosclerosis and Cerebrovascular Disease

Cerebrovascular disease in CKD primarily arises from a synergistic interplay between classical and non-classical mechanisms. The classical risk factors and mechanisms encompass hypertension, diabetes, atrial fibrillation, carotid artery disease, heart failure, obesity, and dyslipidemia, which are all frequently comorbid in CKD. Non-classical risk factors, including chronic inflammation, uremic toxins, reactive oxygen radicals, anemia, and bone mineral disorders, are believed to contribute to the risk of cerebrovascular accidents and CI by inducing vascular injury and endothelial dysfunction [35]. Uremia is considered to promote atherosclerosis through protein carbamylation and contribute to dyslipidemia.

Tasmoc et al. [36] investigated the association between pulse wave velocity (PWV), reflecting arterial stiffness, and cognitive function (TMT, MMSE, etc.) in a study involving 72 HD patients. They reported a significant correlation between elevated PWV values and CI. Additionally, in the COPE study [37], a prospective multicenter cohort study in the Netherlands involving 85 elderly CKD patients including ND and dialysis patients, the relationship between PWV measured by MRI and cognitive function was examined. The study found significant correlations between PWV and all aspects of memory, executive function, and psychomotor speed. In particular, in executive function, a significant association persisted even after adjusting for age, gender, and education.

On the other hand, in the PACE study of 330 dialysis patients [38], it was reported that the augmentation index (AI) and central pulse pressure (cPP), which more notably reflect systemic arterial stiffness than PWV, were significantly associated with CI compared to PWV. Recently, Nishimura et al. [39] reported in a study of 100 HD patients (mean age 67.9 years old, mean history of dialysis 7.3 years) that those with an ankle brachial index (ABI) ≥ 1.06 (n = 69) had significantly higher Montreal Cognitive Assessment (MoCA) scores (25.5 ± 3.9 vs. 22.3 ± 4.6) compared to patients with an ABI < 1.06 (n = 31). Moreover, the ABI and MoCA showed a significant positive correlation in the multiple regression analysis.

These studies suggest that arterial stiffness may be associated with CI and could represent the underlying mechanism of incident CI in elderly CKD patients.

4.2. Hypotension and Decrease of Regional Cerebral Blood Flow during HD

In HD patients, there are specific factors related to HD that influence the risk of cerebrovascular accidents, including cerebral hypoperfusion, enhanced arteriosclerosis, and blood pressure fluctuations [40]. The mean flow velocity of cerebral arteries has been shown to decrease significantly during HD, leading to transient cerebral ischemia and ischemic white matter lesions over time [41].

One of the factors associated with CI in HD is a rapid decrease in blood pressure during HD. Mizumasa et al. [42] conducted a three-year longitudinal study examining the association of rapid hypotension during HD with brain ischemia and brain atrophy using brain MRI. The study revealed a positive association between the total number of rapid hypotension episodes during the HD sessions and the number of lacunar infarctions, along with the degree of frontal lobe atrophy over the three-year period.

In addition, the relationship between decreased regional cerebral blood flow (rCBF) and CI has been reported. Kobayashi et al. [43] examined the cognitive function of rCBF and MMSE measured by SPECT in 54 HD patients, and reported that the rCBF in the middle cerebral artery perfusion region was significantly lower than in other areas in patients with reduced MMSE.

It has also been reported that cerebral oxygen saturation (rSO_2) decreases during HD, as observed using near-infrared spectroscopy (NIRS) [44]. Malik et al. [45] reported that rSO_2 decreased most significantly at 35 min after the initiation of HD. More recently, MacEwen et al. [41] highlighted that the decrease in rSO_2 observed was strongly influenced by the reduction in blood pressure during HD. They found that a decrease in mean blood pressure by 10 mmHg during HD increased the risk of cerebral ischemia (rSO_2 decreased by 15% or more) by 3%, and the risk rose rapidly when the mean blood pressure dropped below 60 mmHg.

Recently, there has been extensive research on the relationship between cerebral ischemia and CI in dialysis patients. The extent of reduction in the mean cerebral blood flow velocity during HD correlates with the degree of cognitive decline and the deterioration of white matter lesions after 12 months. Additionally, the rSO2 of the left frontal lobe, measured by

NIRS, is significantly correlated with the MoCA score. Furthermore, a correlation has been reported between the mixed venous oxygen saturation and MoCA score in the left internal cerebral vein [40][46][47].

4.3. Oxidative Stress

In order to elucidate the mechanism of CI in CKD, researchers conducted the following experiments using CKD mice created through 5/6 nephrectomy. At 8 weeks post-modeling, researchers performed the water maze test and evaluated the learning function of CKD mice compared to sham-operated control mice. Subsequently, researchers conducted pathological and immunohistological examinations using the extracted brains. In the hippocampus of CKD mice, degenerated cells with nuclear condensation (pyknotic cells) appeared along with the accumulation of 8-hydroxy-2′-deoxyguanosine (8-OHdG). The learning ability of CKD mice was significantly decreased in the water maze test. Conversely, in CKD mice administered with an antioxidant (Tempol), the accumulation of 8-OHdG and pyknotic cells in the hippocampus was minimal, and the results of the water maze test were equivalent to those of the control mice [48]. These findings suggest that oxidative stress associated with CKD plays a significant role in neuronal damage in the brain and the decline of learning ability in CI in CKD.

4.4. Insoluble Tau Protein

Recently, Matsuki et al. [49] demonstrated CI in CKD mice. The researchers extracted the hippocampus from both CKD and healthy mice, performing a proteomic analysis by partitioning the hippocampus into soluble and insoluble fractions through salting and salting out. The results indicated increased levels of insoluble tau protein and RNA splicing-related proteins in the brains of CKD mice, akin to findings in Alzheimer’s disease. The study further revealed elevated levels of insoluble phosphorylated tau protein in the hippocampus and cerebral cortex of CKD mice, along with increased immunoglobulin heavy chains. This suggests that the dysfunction of the blood–brain barrier (BBB) enhances substance permeability. Additionally, a multivariable logistic regression analysis of 980 CKD patients, considering CI as the objective variable, identified that elevated blood urea nitrogen and a low nutritional status are strong risk factors for dementia. This implies that the accumulation of urea and other uremic substances is secondarily associated with CI rather than the pure kidney filtration function itself.

References

1. Shimizu, H.; Mori, T.; Yoshida, T.; Tachibana, A.; Ozaki, T.; Yoshino, Y.; Ochi, S.; Sonobe, N.; Matsumoto, T.; Komori, K.; et al. Secular trends in the prevalence of dementia based on a community-based complete enumeration in Japan: The Nakayama Study. Psychogeriatrics 2022, 22, 631–641.
2. Nagata, M.; Ninomiya, T.; Doi, Y.; Yonemoto, K.; Kubo, M.; Hata, J.; Tsuruya, K.; Iida, M.; Kiyohara, Y. Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population: The Hisayama Study. Nephrol. Dial. Transplant. 2010, 25, 2557–2564.
3. Nagai, K.; Asahi, K.; Iseki, K.; Yamagata, K. Estimating the prevalence of definitive chronic kidney disease in the Japanese general population. Clin. Exp. Nephrol. 2021, 25, 885–892.
4. Kurella Tamura, M.; Wadley, V.; Yaffe, K.; McClure, L.A.; Howard, G.; Go, R.; Allman, R.M.; Warnock, D.G.; McClellan, W. Kidney function and cognitive impairment in US adults: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am. J. Kidney Dis. 2008, 52, 227–234.
5. Kurella Tamura, M.; Muntner, P.; Wadley, V.; Cushman, M.; Zakai, N.A.; Bradbury, B.D.; Kissela, B.; Unverzagt, F.; Howard, G.; Warnock, D.; et al. Albuminuria, kidney function, and the incidence of cognitive impairment among adults in the United States. Am. J. Kidney Dis. 2011, 58, 756–763.
6. Kurella Tamura, M.; Yaffe, K.; Hsu, C.Y.; Yang, J.; Sozio, S.; Fischer, M.; Chen, J.; Ojo, A.; DeLuca, J.; Xie, D.; et al. Cognitive Impairment and Progression of CKD. Am. J. Kidney Dis. 2016, 68, 77–83.
7. Kurella Tamura, M.; Gaussoin, S.A.; Pajewski, N.M.; Chelune, G.J.; Freedman, B.I.; Gure, T.R.; Haley, W.E.; Killeen, A.A.; Oparil, S.; Rapp, S.R.; et al. Kidney Disease, Intensive Hypertension Treatment, and Risk for Dementia and Mild Cognitive Impairment: The Systolic Blood Pressure Intervention Trial. J. Am. Soc. Nephrol. 2020, 31, 2122–2132.
8. Wang, H.; Liu, X.; Song, L.; Yang, W.; Li, M.; Chen, Q.; Lv, H.; Zhao, P.; Yang, Z.; Liu, W.; et al. Dysfunctional Coupling of Cerebral Blood Flow and Susceptibility Value in the Bilateral Hippocampus is Associated with Cognitive Decline in Nondialysis Patients with CKD. J. Am. Soc. Nephrol. 2023, 34, 1574–1588.
9. Bugnicourt, J.M.; Godefroy, O.; Chillon, J.M.; Choukroun, G.; Massy, Z.A. Cognitive disorders and dementia in CKD: The neglected kidney-brain axis. J. Am. Soc. Nephrol. 2013, 24, 353–363.

10. Ariton, D.M.; Jiménez-Balado, J.; Maisterra, O.; Pujadas, F.; Soler, M.J.; Delgado, P. Diabetes, Albuminuria and the Kidney-Brain Axis. J. Clin. Med. 2021, 10, 2364.

11. Xie, Z.; Tong, S.; Chu, X.; Feng, T.; Geng, M. Chronic Kidney Disease and Cognitive Impairment: The Kidney-Brain Axis. Kidney Dis. 2022, 8, 275–285.

12. Papageorgiou, C.; Ziroyannis, P.; Vathylakis, J.; Grigoriadis, A.; Hatzikonstantinou, V.; Capsalakis, Z. A comparative study of brain atrophy by computerized tomography in chronic renal failure and chronic hemodialysis. Acta Neurol. Scand. 1982, 66, 378–385.

13. Savazzi, G.M.; Cusmano, F.; Degasperi, T. Cerebral atrophy in patients on long-term regular hemodialysis treatment. Clin. Nephrol. 1985, 23, 89–95.

14. Savazzi, G.M.; Cusmano, F.; Vinci, S.; Allegri, L. Progression of cerebral atrophy in patients on regular hemodialysis treatment: Long-term follow-up with cerebral computed tomography. Nephron 1995, 69, 29–33.

15. Savazzi, G.M.; Cusmano, F.; Musini, S. Cerebral imaging changes in patients with chronic renal failure treated conservatively or in hemodialysis. Nephron 2001, 89, 31–36.

16. Cohen-Hagai, K.; Fanadka, F.; Grumberg, T.; Topaz, G.; Nacasch, N.; Greenberg, M.; Zitman-Gal, T.; Benchetrit, S. Diastolic blood pressure is associated with brain atrophy in hemodialysis patients: A single center case-control study. Ther. Apher. Dial. 2022, 26, 94–102.

17. Cao, M.X.; Xiao, J.; Qin, H.M.; Wang, Z.H.; Boltze, J.; Liu, S.X.; Li, S. Dialysis adequacy and hemoglobin levels predict cerebral atrophy in maintenance-hemodialysis patients. J. Cereb. Blood Flow Metab. 2023, 43, 882–892.

18. Maesato, K.; Ohtake, T.; Mochida, Y.; Ishioka, K.; Oka, M.; Moriya, H.; Hidaka, S.; Kobayashi, S. Correlation of hippocampal atrophy with hyperhomocysteinemia in hemodialysis patients: An exploratory pilot study. PLoS ONE 2017, 12, e0175102.

19. Chen, H.J.; Qiu, J.; Qi, Y.; Fu, L.; Fu, Q.; Wu, W.; Dai, G.; Chen, F. Hippocampal subfield morphology in regular hemodialysis patients. Nephrol. Dial. Transplant. 2023, 38, 992–1001.

20. Vogels, S.C.; Emmelot-Vonk, M.H.; Verhaar, H.J.; Koek, H.L. The association of chronic kidney disease with brain lesions on MRI or CT: A systematic review. Maturitas 2012, 71, 331–336.

21. Kawamura, T.; Umemura, T.; Umegaki, H.; Imamine, R.; Kawano, N.; Mase, H.; Mizoguchi, A.; Minatoguchi, M.; Kusama, M.; Kouchi, Y.; et al. Factors Associated with Changes in Brain Atrophy during a Three-Year Observation in Elderly Diabetic Patients: Effect of Renal Impairment on Hippocampal Atrophy. Dement. Geriatr. Cogn. Dis. Extra. 2016, 6, 55–67.

22. Maki, K.; Ohara, T.; Hata, J.; Shibata, M.; Hirabayashi, N.; Honda, T.; Sakata, S.; Furuta, Y.; Akiyama, M.; Yamasaki, K.; et al. CKD, Brain Atrophy, and White Matter Lesion Volume: The Japan Prospective Studies Collaboration for Aging and Dementia. Kidney Med. 2022, 5, 100593.

23. Grasing, M.; Sharma, P.; Lepping, R.J.; Honea, R.; Burns, J.M.; Brooks, W.M.; Gupta, A.; Alzheimer's Disease Neuroimaging Initiative. Association between the Estimated Glomerular Filtration Rate and Brain Atrophy in Older Adults. Am. J. Nephrol. 2022, 53, 176–181.

24. Yoshimitsu, T.; Hirakata, H.; Fujii, K.; Kanai, H.; Hirakata, E.; Higashi, H.; Kubo, M.; Tanaka, H.; Shinozaki, M.; Katafuchi, R.; et al. Cerebral ischemia as a causative mechanism for rapid progression of brain atrophy in chronic hemodialysis patients. Clin. Nephrol. 2000, 53, 445–451.

25. Taki, Y.; Goto, R.; Evans, A.; Zijdenbos, A.; Neelin, P.; Lerch, J.; Sato, K.; Ono, S.; Kinomura, S.; Nakagawa, M.; et al. Voxel-based morphometry of human brain with age and cerebrovascular risk factors. Neurobiol. Aging 2004, 25, 455–463.

26. Tsuruya, K.; Yoshida, H.; Kuroki, Y.; Nagata, M.; Mizumasa, T.; Mitsuiki, K.; Yoshiura, T.; Hirakawa, M.; Kanai, H.; Hori, K.; et al. Brain atrophy in peritoneal dialysis and CKD stages 3–5, a cross-sectional and longitudinal study. Am. J. Kidney Dis. 2015, 65, 312–321.

27. Tsuruya, K.; Yoshida, H.; Yamada, S.; Haruyama, N.; Tanaka, S.; Tsuchimoto, A.; Eriguchi, M.; Fujisaki, K.; Torisu, K.; Nakano, T.; et al. More rapid progression of brain atrophy in patients on peritoneal dialysis compared with hemodialysis: The VCOHP Study. Hypertens. Res. 2023. ahead of print.

28. Wang, Y.; Zhang, H.X.; Wang, Y.C.; Song, S.H.; Jin, X.Q.; Tian, N.; Chen, M.H. A survey of cognitive function in peritoneal dialysis patients. Ther. Apher. Dial. 2022, 26, 822–826.

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

30. Vollmer, T.; Huynh, L.; Kelley, C.; Galebach, P.; Signorovitch, J.; DiBernardo, A.; Sasane, R. Relationship between brain volume loss and cognitive outcomes among patients with multiple sclerosis: A systematic literature review. Neurol. Sci. 2016, 37, 165–179.
31. Yu, C.C.; Lu, C.Y.; Chen, M.H.; Chen, Y.S.; Lu, C.H.; Lin, Y.Y.; Chou, K.H.; Lin, W.C. Brain Atrophy Mediates the Relationship between Misfolded Proteins Deposition and Cognitive Impairment in Parkinson's Disease. J. Pers. Med. 2021, 11, 702.
32. Chen, Y.; Wang, J.; Cui, C.; Su, Y.; Jing, D.; Wu, L.; Liang, P.; Liang, Z. Evaluating the association between brain atrophy, hypometabolism, and cognitive decline in Alzheimer's disease: A PET/MRI study. Aging 2021, 13, 7228–7246.
33. Tian, N.; Song, L.; Hou, T.; Fa, W.; Dong, Y.; Liu, R.; Ren, Y.; Liu, C.; Zhu, M.; Zhang, H.; et al. Association of Triglyceride-Glucose Index with Cognitive Function and Brain Atrophy: A Population-Based Study. Am. J. Geriatr. Psychiatry 2024, 32, 151–162.
34. Yeh, Y.C.; Kuo, Y.T.; Huang, M.F.; Hwang, S.J.; Tsai, J.C.; Kuo, M.C.; Chen, C.S. Association of brain white matter lesions and atrophy with cognitive function in chronic kidney disease. Int. J. Geriatr. Psychiatry 2019, 34, 1826–1832.
35. Kelly, D.M.; Ademi, Z.; Doehner, W.; Lip, G.Y.H.; Mark, P.; Toyoda, K.; Wong, C.X.; Sarnak, M.; Cheung, M.; Herzog, C.A.; et al. Chronic Kidney Disease and Cerebrovascular Disease: Consensus and Guidance From a KDIGO Controversies Conference. Stroke 2021, 52, e328–e346.
36. Tasmoc, A.; Donciu, M.D.; Veisa, G.; Nistor, I.; Covic, A. Increased arterial stiffness predicts cognitive impairment in hemodialysis patients. Hemodial. Int. 2016, 20, 463–472.
37. Zijlstra, L.E.; Trompet, S.; Jukema, J.W.; Kroft, L.J.M.; de Bresser, J.; van Osch, M.J.P.; Hammer, S.; Witjes, M.N.; van Buren, M.; Mooijaart, S.P. Association of cardiovascular structure and function with cerebrovascular changes and cognitive function in older patients with end-stage renal disease. Aging 2020, 12, 1496–1511.
38. Kim, E.D.; Meoni, L.A.; Jaar, B.G.; Shafi, T.; Linda Kao, W.H.; Estrella, M.M.; Parekh, R.; Sozio, S.M. Association of Arterial Stiffness and Central Pressure with Cognitive Function in Incident Hemodialysis Patients: The PACE Study. Kidney Int. Rep. 2017, 2, 1149–1159.
39. Nishimura, A.; Hidaka, S.; Kawaguchi, T.; Matsukawa, A. Relationship between Lower Extremity Peripheral Arterial Disease and Mild Cognitive Impairment in Hemodialysis Patients. J. Clin. Med. 2023, 12, 2145.
40. Findlay, M.D.; Dawson, J.; Dickie, D.A.; Forbes, K.P.; McGlynn, D.; Quinn, T.; Mark, P.B. Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients. J. Am. Soc. Nephrol. 2019, 30, 147–158.
41. MacEwen, C.; Sutherland, S.; Daly, J.; Pugh, C.; Tarassenko, L. Relationship between hypotension and cerebral ischemia during hemodialysis. J. Am. Soc. Nephrol. 2017, 28, 2511–2520.
42. Mizumasa, T.; Hirakata, H.; Yoshimitsu, T.; Hirakata, E.; Kubo, M.; Kashiwagi, M.; Tanaka, H.; Kanai, H.; Fujimi, S.; Iida, M. Dialysis-related hypotension as a cause of progressive frontal lobe atrophy in chronic hemodialysis patients: A 3-year prospective study. Nephron Clin. Pract. 2004, 97, c23–c30.
43. Kobayashi, S.; Mochida, Y.; Ishioka, K.; Oka, M.; Maesato, K.; Moriya, H.; Hidaka, S.; Ohtake, T. The effects of blood pressure and the renin-angiotensin-aldosterone system on regional cerebral blood flow and cognitive impairment in dialysis patients. Hypertens. Res. 2014, 37, 636–641.
44. Miyazawa, H.; Ookawara, S.; Tabei, K. Aggravation of Cerebral Oxygenation due to Intradialytic Hypotension Induced by Blood Volume Reduction During Hemodialysis: A Case Report. Ther. Apher. Dial. 2015, 19, 525–527.
45. Malik, J.; Kudlicka, J.; Lachmanova, J.; Valerianova, A.; Rocinova, K.; Bartkova, M.; Tesar, V. Tissue ischemia worsens during hemodialysis in end-stage renal disease patients. J. Vasc. Access 2017, 18, 47–51.
46. Kovarova, L.; Valerianova, A.; Kmentova, T.; Lachmanova, J.; Hladinova, Z.; Malik, J. Low Cerebral Oxygenation Is Associated with Cognitive Impairment in Chronic Hemodialysis Patients. Nephron 2018, 139, 113–119.
47. Chai, C.; Wang, H.; Chu, Z.; Li, J.; Qian, T.; Mark Haacke, E.; Xia, S.; Shen, W. 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. 2020, 14, 1339–1349.
48. Fujisaki, K.; Tsuruya, K.; Yamato, M.; Toyonaga, J.; Noguchi, H.; Nakano, T.; Taniguchi, M.; Tokumoto, M.; Hirakata, H.; Kitazono, T. Cerebral oxidative stress induces spatial working memory dysfunction in uremic mice: Neuroprotective effect of tempol. Nephrol. Dial. Transplant. 2014, 29, 529–538.
49. Matsuki, H.; Mandai, S.; Shiwaku, H.; Koide, T.; Takahashi, N.; Yanagi, T.; Inaba, S.; Ida, S.; Fujiki, T.; Mori, Y.; et al. Chronic kidney disease causes blood-brain barrier breakdown via urea-activated matrix metalloproteinase-2 and insolubility of tau protein. Aging 2023, 15, 10972–10995.