EXCELLENCIA
INTERNATIONAL MULTI-DISCIPLINARY JOURNAL OF EDUCATION
Volume 02, Issue 09, 2024 ISSN (E): 2994-9521

Specific Risk Factors for Development Cerebrovascular Disorders in Patients with Chronic Kidney Disease

Xaydarova Dildora Kodirovna [1], Kudratova Shaxodat Ramazonovna [2]

[1] Associate Professor of Neurology, Tashkent Medical Academy

[2] PhD, Assistant of the Department of Neurology, Bukhara State Medical Institute

Abstract:

Cerebral vascular disorders are one of the leading causes of disability and mortality in patients with chronic kidney disease (CKD). The article presents the currently available data on risk factors (RF) for the development of cerebrovascular disorders in pre-dialysis patients with CKD. Two groups of RF are identified: traditional and non-traditional (specific). Traditional RF, which include arterial hypertension, diabetes mellitus and hypercholesterolemia, independently affect the cerebral vascular bed and get worse against the background of CKD. Specific RF is associated with features of the CKD pathogenesis. It includes increased blood levels of homocysteine, β2-microglobulin, impaired calcium-phosphorus metabolism, accumulation of uremic toxins and toxins of intestinal bacteria, anemia and other factors. In the present review, special attention is paid to specific RF and pathogenetic mechanisms of the development of cerebrovascular disorders in predialysis patients with CKD.

Keywords: chronic kidney disease, cerebrovascular disorders, stroke, hyperhomocysteinemia, uremic toxins, intestinal bacteria toxins, impaired calcium-phosphorus metabolism.

Chronic kidney disease (CKD) is associated with alterations of vascular functions, blood chemistry, and red blood cell production [1]. These dysfunctions impair blood perfusion, and this can subsequently affect brain functions. Indeed, cerebrovascular diseases are common in CKD patients, who display an increased rate of cognitive disorders and dementia [2,3] and a greater burden of abnormal brain white matter disease [4]. Cognitive impairments in CKD can be partly related to vascular dementia, as dialysis patients with cognitive disorders also present numerous cortical ischemic lesions [5–7]. Indeed, the risk of transient ischemic attack and stroke increases with progressive kidney function decline [8–12] and stroke in these patients is associated with more severe neurological deterioration, poorer functional recovery [13,14], and increased mortality [15,16].

Endothelial dysfunction (ED), one of the first steps in the development and progression of atherosclerosis, is considered a non-traditional CV risk factor in CKD and its prevalence progressively increases as the disease progresses to end stage kidney disease. ED is evident at an early stage in CKD patients, occurs independently of hypertension development and contributes to arterial stiffness and to renal interstitial fibrosis [15–17]. In addition to chronic inflammation and oxidative stress, hemodynamic disturbances, and the continuous exposure to uremic toxins in CKD, may result in an imbalance between endothelial injury and repair that progressively worsens as renal function deteriorates [18]. The assessment of ED was found to be useful to predict cardiovascular events, not only in the general population but also in high-risk groups [9,10]. Forearm reactive hyperemia has been considered a gold-standard measure of macrovascular endothelial function that proved to correlate well with invasively measured coronary ED [11,12]. However, this technique has been criticized for lack of reproducibility because it is highly operator dependent. Recently, reactive hyperemia index (RHI) derived from peripheral arterial tonometry (PAT) has gained wide acceptance in the scientific community because it is a noninvasive and non-operator dependent method for assessment of microvascular function, that has been validated for stratification in both low-risk and high-risk populations [17,19]. The occurrence of cerebrovascular disorders may be linked to the presence of traditional and non-traditional cardiovascular risk factors in CKD. Here, we review current knowledge on the epidemiological aspects of CKD-associated neurological and cognitive disorders and discuss putative causes and potential treatment. CKD is associated with traditional (hypertension, hypercholesterolaemia, diabetes etc.) and non-traditional cardiovascular risk factors such as elevated levels of oxidative stress, chronic inflammation, endothelial dysfunction, vascular calcification, anaemia and uraemic toxins. Clinical and animal studies indicate that these factors may modify the incidence and/or outcomes of stroke and are associated with white matter diseases and cognitive impairment. However, direct evidence in CKD patients is still lacking. A better understanding of the factors responsible for the elevated prevalence of cerebrovascular diseases in CKD patients may facilitate the development of novel treatments. Very few clinical trials have actually been performed in CKD patients, and the impact of certain treatments is subject to debate. Treatments that lower LDL cholesterol or blood pressure may reduce the incidence of cerebrovascular diseases in CKD patients, whereas treatment with erythropoiesis-stimulating agents may be associated with an increased risk of stroke but a decreased risk of cognitive disorders. The impact of therapeutic approaches that reduce levels of uraemic toxins has yet to be evaluated. [23].

Among dialysis patients, stroke risks are particularly high. One study that leveraged the National Health Insurance program database in Taiwan compared more than 80,000 dialysis patients with general population controls; these investigators described a nearly threefold increased risk of ischemic stroke and a six-fold increased risk of hemorrhagic stroke as compared with the general population after controlling for risk factors[26]. Within the dialysis population, peritoneal dialysis patients were at slightly lower risk of hemorrhagic stroke than matched hemodialysis patients. This study, however, may have limited generalizability because stroke rates may be higher among Asian populations. In a large single-center study of 2,384 hemodialysis patients in the United Kingdom, the incident stroke rate was 15 per 1000 patient years, an incidence similar to that seem in the Taiwan study, with major risk factors including diabetes and hypertension. Cerebrovascular disease is unlikely to be the only contributing factor to cognitive impairment in individuals with CKD because cognitive performance steadily worsens as kidney function declines5 and then often improves with kidney transplantation.[22,23] Longitudinal studies evaluating cognitive function pre- and posttransplantation show improvement in cognitive function within the first 6 to 12 months posttransplantation, with improved function still apparent several years later, though such improvement may be modified by frailty.[22–24] The potential explanations of this finding are 2-fold: first, successful transplantation restores crucial functions of the kidney, such as filtration, secretion, tubular function, hormonal balance (that are not replicated by dialysis), and clearance of medications, both of which may be essential for optimal cognitive function; and second, transplantation eliminates the need for dialysis and the associated complications that may promote cognitive impairment, particularly with hemodialysis, such as sudden hemodynamic shifts, routine use of anticoagulation that may predispose to microbleeds, and intermittent rather than continual solute clearance.

Several observations suggest that CKD and kidney replacement therapy are associated with chronic inflammation. Plasma concentrations of C-reactive protein, fibrinogen, interleukin-6, and other inflammatory markers occur in patients with CKD and in those with ESRD.18 CKD is also associated with activation of platelet adhesion molecules and alterations in the structure and concentration of lipoproteins.18 Often chronic inflammation is associated with evidence of malnutrition, particularly in ESRD patients maintained on dialysis.[34] However, because systemic inflammation is a risk factor for stroke risk in other populations, it is plausible that systemic inflammation by itself also contributes to the higher risk of stroke in patients with CKD.[35]

Chronic kidney disease independently increases the risk of stroke and the burden of ischemic small vessel disease. In this study, the presence of stage 3 or higher CKD was associated with increased distal resistance in the anterior cerebral circulation of post-stroke patients. Anterior circulation and posterior circulation distal resistive indices also correlated with the degree of SVD on MRI. Prospective TCD studies assessing intracranial PI and MFV changes and white matter disease burdens in larger samples may be helpful for noninvasive screening and informing risk factor modification in patients with CKD at high risk for neurovascular disease

References

1. Barsoum, R.S. Chronic kidney disease in the developing world. N. Engl. J. Med. 2006, 354, 997–999. [CrossRef] [PubMed]
2. Nugent, R.A.; Fathima, S.F.; Feigl, A.B.; Chyung, D. The burden of Chronic Kidney Disease on developing nations: A 21st century challenge in global health. Nephron Clin. Pract. 2011, 118, c269–c277. [CrossRef] [PubMed]
3. Manjunath, G.; Tighiouart, H.; Ibrahim, H.; MacLeod, B.; Salem, D.N.; Griffith, J.L.; Coresh, J.; Levey, A.S.; Sarnak, M.J. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. J. Am. Coll. Cardiol. 2003, 63, 1121–1129. [CrossRef]
4. Anavekar, N.S.; Pfeffer, M.A. Cardiovascular risk in chronic kidney disease. Kidney Int. 2004, 66, S11–S15. [CrossRef]
5. Go, A.S.; Chertow, G.M.; Fan, D.; McCulloch, C.E.; Hsu, C.Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N. Engl. J. Med. 2004, 351, 1296–1305. [CrossRef] [PubMed] Life 2021, 11, 210 11 of 12
6. Sarnak, M.J.; Levey, A.S.; Schoolwerth, A.C.; Coresh, J.; Culleton, B.; Hamm, L.L.; McCullough, P.A.; Kasiske, B.L.; Michael, E.K.; Klag, J.; et al. Wilson Kidney Disease as a Risk Factor for Development of Cardiovascular Disease. Circulation 2003, 108, 2154–2169. [CrossRef]
7. Irie, F.; Iso, H.; Sairenchi, T.; Fukasawa, N.; Yamagishi, K.; Ikehara, S.; Kanashiki, M.; Saito, Y.; Ota, H.; Nose, T. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. Kidney Int. 2006, 69, 1264–1271. [CrossRef]

8. Kuo, C.C.; Lee, C.T.; Ho, S.C.; Kuo, H.W.; Wu, T.N.; Yang, C.Y. Haemodialysis and the risk of stroke: A population-based cohort study in taiwan, a country of high incidence of end-stage renal disease. Nephrology 2012, 17, 243–248. [CrossRef] [PubMed]
9. El Husseini, N.; Kaskar, O.; Goldstein, L.B. Chronic kidney disease and stroke. Adv. Chronic Kidney Dis. 2014, 21, 500–508. [CrossRef] [PubMed]
10. Toyoda, K.; Ninomiya, T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. Lancet Neurol. 2014, 13, 823–833. [CrossRef]
11. Hojs Fabjan, T.; Hojs, R. Stroke and renal dysfunction. Eur. J. Intern. Med. 2014, 25, 18–24. [CrossRef] [PubMed]
12. Koren-Morag, N.; Goldbourt, U.; Tanne, D. Renal dysfunction and risk of ischemic stroke or tia in patients with cardiovascular disease. Neurology 2006, 67, 224–228. [CrossRef] [PubMed]
13. Kumai, Y.; Kamouchi, M.; Hata, J.; Ago, T.; Kitayama, J.; Nakane, H.; Sugimori, H.; Kitazono, T. Proteinuria and clinical outcomes after ischemic stroke. Neurology 2012, 78, 1909–1915. [CrossRef] [PubMed]
14. Sozio, S.M.; Armstrong, P.A.; Coresh, J.; Jaar, B.G.; Fink, N.E.; Plantinga, L.C.; Powe, N.R.; Parekh, R.S. Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: The choices for healthy outcomes in caring for esrd (choice) study. Am. J. Kidney Dis. 2009, 54, 468–477. [CrossRef] [PubMed]
15. Hojs Fabjan, T.; Hojs, R.; Tetickovic, E.; Pecovnik Balon, B. Ischaemic stroke–impact of renal dysfunction on in-hospital mortality. Eur. J. Neurol. 2007, 14, 1351–1356. [CrossRef] [PubMed]
16. Tsagalis, G.; Akrivos, T.; Alevizaki, M.; Manios, E.; Stamatellopoulos, K.; Laggouranis, A.; Vemmos, K.N. Renal dysfunction in acute stroke: An independent predictor of long-term all combined vascular events and overall mortality. Nephrol. Dial. Transplant. 2009, 24, 194–200. [CrossRef] [PubMed]
17. Allen, C.L.; Bayraktutan, U. Oxidative stress and its role in the pathogenesis of ischaemic stroke. Int. J. Stroke 2009, 4, 461–470. [CrossRef] [PubMed]
18. Yu, G.; Liang, Y.; Zheng, S.; Zhang, H. Inhibition of myeloperoxidase by n-acetyl lysyltyrosylcysteine amide reduces oxidative stress-mediated inflammation, neuronal damage, and neural stem cell injury in a murine model of stroke. J. Pharmacol. Exp. Ther. 2018, 364, 311–322. [CrossRef] [PubMed]
19. Watanabe A. Cerebral microbleeds and intracerebral hemorrhages in patients on maintenance hemodialysis. J Stroke Cerebrovasc Dis 2007; 16: 30–33
20. Yokoyama S, Hirano H, Uomizu K et al. High incidence of microbleeds in hemodialysis patients detected by T2*-weighted gradient-echo magnetic resonance imaging. Neurol Med Chir (Tokyo) 2005; 45: 556–560
21. Naganuma T, Takemoto Y, Yamasaki T et al. Factors associated with silent cerebral microbleeds in hemodialysis patients. Clin Nephrol 2011; 75: 346–355
22. Murray AM, Seliger S, Lakshminarayan K et al. Incidence of stroke before and after dialysis initiation in older patients. J Am Soc Nephrol 2013; 24: 1166–1173 23. Madero M, Sarnak MJ. Does hemodialysis hurt the brain? Semin Dial 2011; 24: 266–268
23. Toyoda K, Fujii K, Ando T et al. Incidence, etiology, and outcome of stroke in patients on continuous ambulatory peritoneal dialysis. Cerebrovasc Dis 2004; 17: 98–105
24. Hojs Fabjan T, Hojs R. Stroke and renal dysfunction. Eur J Intern Med 2014; 25: 18–24

25. Koren-Morag N, Goldbourt U, Tanne D. Renal dysfunction and risk of ischemic stroke or TIA in patients with cardiovascular disease. Neurology 2006; 67: 224–228

26. Stang, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur. J. Epidemiol. 2010, 25, 603–605. [CrossRef] [PubMed]

27. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. Controlled Clin. Trials 1986, 7, 177–188. [CrossRef] [PubMed] Medicines 2023, 10, 46 14 of 14 29. Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. BMJ 2003, 327, 557–560. [CrossRef] [PubMed]

28. Easterbrook, P.J.; Gopalan, R.; Berlin, J.; Matthews, D.R. Publication bias in clinical research. Lancet 1991, 337, 867–872. [CrossRef]

29. FONG, V.; Kamaruzaman, L.; Daud, W.W.; Mohd, R.; Tan, H.; Erica, Y.; Mustafar, R. POS-617 contrast-induced encephalopathy in a patient with end-stage renal disease. Kidney Int. Rep. 2022, 7, S264. [CrossRef]

30. Egger, M.; Smith, G.D.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997, 315, 629–634. [CrossRef]

31. Murumkar, V.; Peer, S.; Jabeen, S.; Chauhan, R.S.; Saini, J.; Aravinda, R.H.; Lanka, V.; Kulkarni, G.B. Contrast-Induced Encephalopathy—An Unusual Complication Following Endovascular Interventions in the Anterior Circulation. Ann. Indian Acad. Neurol. 2021, 24, 635–639. [CrossRef] [PubMed]

32. Hamra, M.; Bakhit, Y.; Khan, M.; Moore, R. Case report and literature review on contrast-induced encephalopathy. Future Cardiol. 2017, 13, 331–335. [CrossRef] [PubMed]

33. Pokersnik, J.A.; Liu, L.; Simon, E.L. Contrast-induced encephalopathy presenting as acute subarachnoid hemorrhage. Am. J. Emerg. Med. 2018, 36, 1122.e3–1122.e4. [CrossRef] [PubMed]

34. Mescolotte, G.M.; Silva, F.R.D.; Afonso, S.; Pamplona, J.; Moreno, R. Reversible contrast-induced encephalopathy after coil embolization of epistaxis. Rev. Bras. Ter. Intensiva 2021, 33, 331–335. [CrossRef] [PubMed]

35. Senthilkumaran, S.; Balamurugan, N.; Jena, N.N.; Thirumalaikolundusubramanian, P. Contrast-induced encephalopathy and diagnostic modalities—Can it make a difference? Am. J. Emerg. Med. 2018, 36, 2328. [CrossRef]

36. Ramalho, J.; Semelka, R.C.; Ramalho, M.; Nunes, R.H.; AlObaidy, M.; Castillo, M. Gadolinium-Based Contrast Agent Accumulation and Toxicity: An Update. AJNR Am. J. Neuroradiol. 2016, 37, 1192–1198. [CrossRef]