Hypertension Research (2024) 47:1090–1091
https://doi.org/10.1038/s41440-024-01599-6

COMMENT

CKD could be a new risk factor of dementia

Kei Kamide[1]

Keywords CKD · dementia · cognitive impairment

Received: 12 November 2023 / Revised: 2 January 2024 / Accepted: 13 January 2024 / Published online: 9 February 2024

In countries where the population is aging, the incidence of dementia is increasing significantly, and it has become a huge public health problem [1]. As the disease is irreversible once it progresses, it is important to prevent dementia and its progression. In order to prevent dementia, it is essential to control its risk factors as much as possible during the normal period and at the stage of mild cognitive impairment. So what is the risk of dementia?

Very well-known the 2020 Lancet commission on dementia prevention report [1] which identified 12 modifiable risk factors, including less education, hearing loss, traumatic brain injury, hypertension, excess alcohol drinking, obesity, smoking, depression, social isolation, physical inactivity, air pollution, and diabetes have been reported, and it has been shown that preventing and improving these can reduce the risk by 40% (Table 1). However, it is not yet clear how to reduce the risk by improving the remaining 60%.

Arafa A and colleagues now show that chronic kidney disease (CKD) is an independent risk factor for cognitive impairment in the Suita Study, a cohort study of the general community-dwelling population [2]. This study found that even after adjusting for age, gender, and other factors known to be risk factors for dementia, such as smoking, alcohol consumption, hypertension, diabetes, and obesity, the risk of developing cognitive dysfunction increases as estimated GFR declines. When an estimated GFR of 45 to 60 is considered mild CKD and less than 45 is considered moderate to severe CKD, the risk of cognitive impairment with an MMSE score of 26 or less is 1.49 and 2.35, respectively, indicating that the odds ratio increases with a decrease in GFR [2].

The relationship between CKD and dementia has been investigated so far. According to a very well-known meta-analysis, when CKD was estimated to be less than 60, the association with dementia, Alzheimer's disease, and cognitive impairment combined was marginal but not significant with an odds ratio of 1.28 and a 95% confidence interval of 0.95–1.28 ($p = 0.063$). In contrast, there was a significant association with albuminuria, with an odds ratio of 1.35 (1.06–1.73, $p = 0.015$) [3].

In the current report by Arafa et al. [2], the association between proteinuria and cognitive dysfunction was not significant. It is unclear as the details are not described, but it is likely that the results are based on the relationship between the qualitative results of proteinuria in urine tests and MMSE scores, and the discrepancy between the results and the meta-analysis is likely because the evaluation was not based on quantitative microalbuminuria. There is another report that cognitive function declines with increased albuminuria [4]. Therefore, it is inferred that mild vascular disorder could be important as a common pathological condition of CKD and cognitive dysfunction, but this is unclear in this report [2], and more detailed analysis including microalbuminuria data will be required in the future.

Blood vessel damage occurs in both CKD and the brain, and may have an impact on CKD and cognitive dysfunction. Another possible mechanism is that the anemia that occurs with the progression of CKD contributes to the development of cognitive dysfunction [5]. Furthermore, recent experimental studies using mice showed that a brain proteomic signature of CKD indicating BBB breakdown and insolubility of tau protein, which are pathologically linked to Alzheimer's disease. Urea-mediated activation of MMP2 was partially responsible for blood-brain barrier breakdown in CKD [6]. This seems to be a finding that leads to a relationship between CKD and dementia.

✉ Kei Kamide
kamide@sahs.med.osaka-u.ac.jp

[1] Division of Health Sciences, Osaka University Graduate School of Medicine, Suita, Japan

Table 1 Potential modifiable risk factors for dementia and cognitive impairment [1]

Early life	less education
Midlife	hearing loss traumatic brain injury hypertension excess alcohol drinking obesity
Later life	smoking depression social isolation physical inactivity air pollution diabetes
New candidate **Midlife-Later life**	CKD (eGFR < 60 ml/min/1.73 m^2)

Although the findings revealed this time are observational study cohorts and the mechanisms are not known, they are highly reliable as they were obtained from data on over 6000 general residents aged 50 and over, and they are associated with CKD and cognitive dysfunction in Japanese people. There is no doubt that there is a relationship between the two. Based on this report, we propose to add CKD as a risk factor for dementia and cognitive dysfunction (Table 1). Since the age range of study participants in this report was above 50 years and more, CKD might be a new candidate of the risk factor for cognitive decline from midlife until later life. In Japan, countermeasures against CKD are being promoted through end-stage renal disease including dialysis and prevention of ischemic heart disease and heart failure [7], but in a country where the population is rapidly aging, developing countermeasures against CKD based on the prevention of dementia might be the key to extending the healthy life expectancy.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396:413–46.
2. Arafa A, Kawachi H, Matsumoto C, Teramoto M, Yasui Y, Kato Y, et al. The association between the estimated glomerular filtration rate and cognitive impairment: the Suita Study. Hypertens Res 2024 https://doi.org/10.1038/s41440-023-01476-8.
3. Deckers K, Camerino I, van Boxtel MPJ, Verhey FRJ, Irving K, Brayne C, et al. Dementia risk in renal dysfunction: A systematic review and meta-analysis of prospective studies. Neurology 2017;88:198–208.
4. Yeh T-S, Clifton L, Collister JA, Liu X, Hunter DJ, Littlejohns TJ. Kidney function, albuminuria, and their modification by genetic factors and risk of incident dementia in UK Biobank. Alzheimers Res Ther. 2023;15:138.
5. Koyama AK, Nee R, Yu W, Choudhury D, Heng F, Cheung AK, et al. Role of Anemia in Dementia risk among veterans with incident CKD. Am J Kidney Dis. 2023;S0272-6386:00735–7.
6. Matsuki H, Mandai S, Shiwaku H, Koide T, Takahashi N, Yanagi T, et al. Chronic kidney disease causes blood-brain barrier breakdown via urea-activated matrix metalloproteinase-2 and insolubility of tau protein. Aging. 2023;15:10972–95.
7. Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012. Edited by Japanese Society of Nephrology, Tokyo Igakusya Inc. (in Japanese).