Hypertension Research (2022) 45:1082–1084
https://doi.org/10.1038/s41440-022-00906-3

COMMENT

Is unrecognized cognitive impairment in hypertension unmasked by diabetes mellitus?

Michiaki Nagai[1] · Keigo Dote[1] · Carola Yvette Förster[2]

Received: 22 February 2022 / Accepted: 28 February 2022 / Published online: 8 April 2022

While hypertension (HT) is commonly associated with white matter lesions that are a cause of vascular dementia (VaD), the relationship of midlife HT with VaD and Alzheimer's disease (AD) has also been shown [1].

Mild cognitive impairment (MCI) is regarded as a transition phase between healthy cognitive aging and dementia, and its identification can lead to secondary prevention by controlling the risks for cardiovascular diseases, including HT and diabetes mellitus (DM) [2]. Based on the neuropsychological profile, two main subtypes of MCI can be distinguished. One is "amnestic type MCI", which may progress preferentially to AD, and the other is "multiple domain type MCI", which may progress to not only AD but also VaD or may even represent a cognitive aging process qualified as normal [2, 3]. In the analysis of the Alzheimer's Disease Neuroimaging Initiative, subjects with MCI progressed to AD in 12 months at a rate of 16.5% per year [3]. Additionally, metabolic syndrome was associated with a higher risk of MCI and progression from MCI to dementia, particularly VaD [4].

The paper by Yamamoto et al. [5] in this issue of the *Journal* provides several new insights into the unrecognized cognitive impairment in an analysis of data from the Cognitive impairment in HypERtensive individuals in ambulatoRY care (Cherry) study of 312 elderly hypertensive patients who were not previously diagnosed with cognitive impairment. Approximately one-third of the elderly patients who received antihypertensive agents were found to have unrecognized cognitive impairment. When the extracted data from MCI patients who received antihypertensive agents from the Organized Registration for the Assessment of dementia on Nation-wide General consortium toward Effective treatment in Japan (ORANGE) registry were compared, the hypertensive patients with unrecognized cognitive impairment in the Cherry study had a larger number of antihypertensive agents and a higher prevalence of DM than MCI patients in the ORANGE registry, while blood pressure (BP) levels between the two groups were equivalent. Although the clinical expression of unrecognized cognitive impairment in elderly hypertensive patients reported by Yamamoto et al. [5] might be different from that in MCI, we can hypothesize that these two types of cognitive impairment share a common pathophysiological basis.

The concept of vascular cognitive impairment (VCI) includes a prestage of VaD. The term VCI characterizes all forms of cognitive deficits from MCI of vascular origin to VaD. The mild form of VCI is defined as vascular MCI, and the most severe form is VaD [6]. In the Tajiri & Kurihara projects, community-dwelling elderly individuals with vascular MCI were shown to be usually unrecognized and were not clinically identified until they developed obvious dementia. The elderly individuals with unrecognized vascular MCI tended to have a decreased ability to follow their medication regimens, and this poor adherence worsened vascular comorbidities [7].

Subcortical small-vessel disease (SSVD) is considered the most prevalent ischemic cerebral disorder and has been associated with HT and DM [8]. Increased BP variability as well as chronic kidney disease were also shown to be determinants of SSVD [9, 10]. The hallmark of SSVD is ischemic white matter lesions, which can present as lacunar infracts and global brain hypoperfusion in a common and homogeneous subtype of VCI, which is often unrecognized. Brain imaging has resulted in substantially advanced diagnostic tools for SSVD. Vascular MCI patients with SSVD exhibit more pronounced impairments in executive function. The Montreal Cognitive Assessment performed better than the Mini-Mental State Examination (MMSE) in detecting MCI with SSVD [8]. Although there were no

✉ Michiaki Nagai
nagai10m@r6.dion.ne.jp

[1] Department of Cardiology, Hiroshima City Asa Hospital, Hiroshima, Japan

[2] Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, Würzburg, Germany

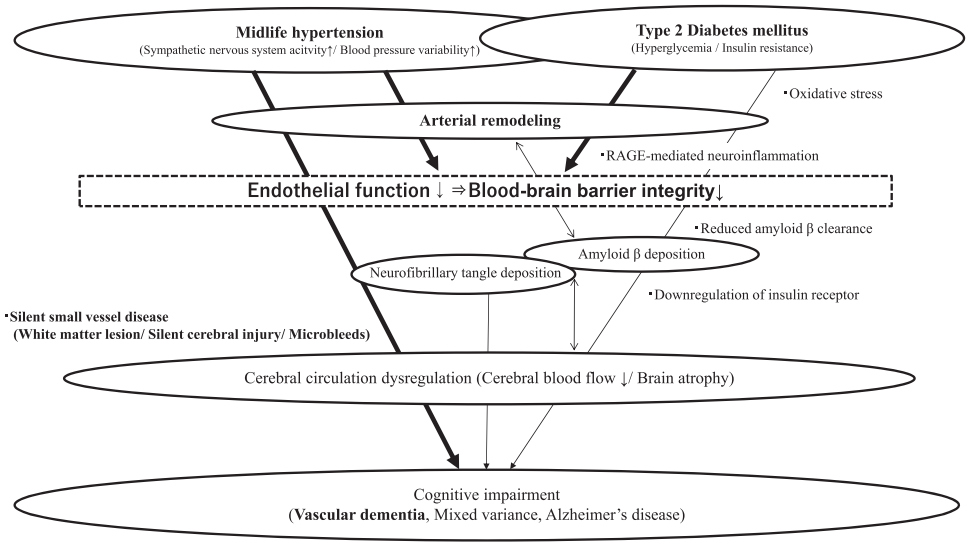

Fig. 1 Common pathophysiology for VaD and AD. The factors of hypertension and diabetes mellitus are both associated with reduced blood–brain barrier integrity and cerebral circulation dysregulation. This could act as a common pathophysiology for silent small vessel disease and brain atrophy. Comorbid hypertension and diabetes mellitus in unrecognized cognitive impairment might be more strongly associated with VCI factors than with neurodegenerative disease factors. AD Alzheimer's disease, VaD vascular dementia, VCI vascular cognitive impairment, RAGE receptor for advanced glycation end products

brain imaging data in the Cherry study, the clinical form of unrecognized cognitive impairment in elderly hypertensive patients reported by Yamamoto et al. [5] might be similar to that in vascular MCI.

Endothelial dysfunction, blood–brain barrier (BBB) disruption, and neurovascular unit dysfunction have been suggested as initial pathogenetic features in both VaD and AD, which could provide a link between arterial remodeling and AD [2]. Cerebral hypoperfusion due to arterial remodeling enhances the production of amyloid beta (Aβ). Arterial stiffening as well as microvascular dysfunction impair Aβ clearance and elevate brain Aβ levels [11]. Increased large arterial stiffness due to exposure to long-standing HT might provide a direct effect on the cerebral penetrating arteries associated with altered structure and function. Subsequently, this process has a harmful role in transporting perivascular Aβ from the brain along the perivascular space via cerebrospinal fluid drainage [11]. Thus, a disruption of vascular dynamics and reduced perivascular flow of Aβ causes decreased Aβ clearance. As a consequence, arterial remodeling has a relationship with cerebral Aβ deposition [11].

DM has detrimental effects on the vasculature, resulting in the development of various cardiovascular diseases stemming from microvascular injury. The BBB is a highly specialized structure protecting the unique microenvironment of the brain. Endothelial cells, which are connected by junctional complexes and express numerous transporters, constitute the main cell type in the BBB. A high-fat diet in mice has been shown to downregulate glucose transporter (GLUT)-1 expression in BBB vascular endothelial cells and reduce brain glucose uptake [12]. Myeloid cell-specific deletion of VEGF in VEGF (Δmyel) mice impairs BBB-GLUT1 expression, brain glucose uptake, and memory formation in obese mice. Obese VEGF (Δmyel) mice exhibit an exaggerated progression of cognitive decline and neuroinflammation on an AD background without increasing $A\beta_{1-42}$ processing or plaque burden [12]. DM patients with unrecognized cognitive impairment had a significantly reduced hippocampal volume compared with cognitively normal DM patients in the voxel-based morphometry for AD [13].

The issue of whether the interaction of HT with DM will increase the risk of cognitive decline remains incompletely understood. MMSE scores over 6 years declined at a steeper rate for elderly individuals comorbid with HT and DM than for those with neither or only one of the conditions [14]. In the Kungsholmen project [15], severe HT combined with DM significantly increased the risk of dementia, VaD, and AD during the 6-year follow-up. The adjusted hazard ratios related to the interaction between severe HT and DM were 3.0 for dementia, 11.3 for VaD, and 2.6 for AD [15]. Because the hypertensive patients with unrecognized cognitive impairment in the Cherry study had a higher prevalence of DM, there might be patients whose unrecognized cognitive impairment transfers to VaD, AD or mixed variants [5].

From these perspectives, DM might also serve as a potential mediator for the relationship between HT and unrecognized cognitive impairment (Fig. 1). The data presented in the manuscript by Yamamoto et al [5]. could have much more importance if the underlying mechanism based

on brain imaging and the prognosis of conversion to dementia could be determined.

Funding DFG grant Fo 315/5-1 to CYF and a grant by the fundation Forschung hilft to CYF.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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

References

1. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4:487–99.
2. Nagai M, Hoshide S, Kario K. Hypertension and dementia. Am J Hypertens. 2010;23:116–24.
3. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology 2010;74:201–9.
4. Tahmi M, Palta P, Luchsinger JA. Metabolic syndrome and cognitive function. Curr Cardiol Rep. 2021;23:180.
5. Yamamoto K, Akasaka H, Yasunobe Y, Shimizu A, Nomoto K, Nagai K, et al. Cherry study group. Clinical characteristics of older adults with hypertension and unrecognized cognitive impairment. Hypertens Res. 2022;45:612–9.
6. Van der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CLH, et al. Vascular cognitive impairment. Nat Rev Dis Prim. 2018;4:18003.
7. Meguro K, Dodge HH. Vascular mild cognitive impairment: Identifying disease in community-dwelling older adults, reducing risk factors, and providing support. The Osaki-Tajiri and Kurihara Projects. J Alzheimers Dis. 2019;70:S293–S302.
8. Wallin A, Román GC, Esiri M, Kettunen P, Svensson J, Paraskevas GP, et al. Update on vascular cognitive impairment associated with subcortical small-vessel disease. J Alzheimers Dis. 2018;62:1417–41.
9. Nagai M, Kario K. Visit-to-visit blood pressure variability, silent cerebral injury, and risk of stroke. Am J Hypertens. 2013;26:1369–76.
10. Nagai M, Hoshide S, Takahashi M, Shimpo M, Kario K. Sleep duration, kidney function, and their effects on cerebral small vessel disease in elderly hypertensive patients. Am J Hypertens. 2015;28:884–93.
11. Nagai M, Dote K, Kato M, Sasaki S, Oda N, Kagawa E, et al. Visit-to-visit blood pressure variability and Alzheimer's disease: links and risks. J Alzheimers Dis. 2017;59:515–26.
12. Jais A, Solas M, Backes H, Chaurasia B, Kleinridders A, Theurich S, et al. Myeloid-cell-derived VEGF maintains brain glucose uptake and limits cognitive impairment in obesity. Cell. 2016;165:882–95.
13. Ueba Y, Murakami T, Yamamoto T, Kuroe A, Yamasaki M, Kaneda D, et al. Voxel-based specific regional analysis system for Alzheimer's disease utility as a screening tool for unrecognized cognitive dysfunction of elderly patients in diabetes outpatient clinics: multicenter retrospective exploratory study. J Diabetes Investig. 2022;13:177–84.
14. Hassing LB, Hofer SM, Nilsson SE, Berg S, Pedersen NL, McClearn G, et al. Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. Age Ageing. 2004;33:355–61.
15. Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L. Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. Neurology. 2004;12:1181–86.