Received: 16 February 2022 | Revised: 16 February 2022 | Accepted: 16 February 2022

DOI: 10.1111/jch.14452

COMMENTARY

WILEY

When cognitive impairment has a vascular origin

Simona Lattanzi MD, PhD[1] | **Afshin A. Divani PhD**[2] | **Francesco Brigo MD**[3]

[1]Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy

[2]Department of Neurology, University of New Mexico, New Mexico, USA

[3]Division of Neurology, "Franz Tappeiner" Hospital, Merano (BZ), Italy

Correspondence
Simona Lattanzi, Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Via Conca 71, Ancona 60020, Italy.
Email: alfierelattanzisimona@gmail.com

Funding information
There are no funders for this work.

In the current issue of *The Journal of Clinical Hypertension*, the study by Dr. Zuo and colleagues aimed to explore the risk factors of cognitive decline in patients with a transient ischemic attack (TIA) or stroke.[1] Among 15 166 patients of the Third China National Stroke Registry (CNSR-III) database, 2283 participants from the impairment of cognition and sleep quality (ICONS) subgroup were included in the study. Patients had a mean age of 61 years, 73% were males, and 63% had a history of hypertension with a median disease duration of 10 years. Trained psychologists assessed the cognitive function of patients at 2 weeks and 3 months from the onset of TIA/stroke using the Montreal Cognitive Assessment–Beijing. Deterioration of cognitive functions, which was defined as the decline of two or more points in the MoCA-Beijing score at the follow-up visit, occurred in 292 (12.8%) patients and was significantly associated with a history of hypertension.[1]

Poststroke cognitive impairment refers to cognitive deterioration that develops after stroke, can range from mild deficit to dementia, and represents a common and major long-term sequela of stroke.[2,3] The prevalence of dementia at 3 months from stroke onset in patients aged over 60 years was found to be nine-fold higher than in controls.[4] Poststroke cognitive impairment is closely related to disability, dependency, and institutionalization, and it is a major determinant of return to work and quality of life in stroke survivors.[5–7] This clinical condition has increasingly gained attention due to the high prevalence and implication on health. The research aimed at better understanding and preventing it is a priority for patients, carers, and clinicians.[8,9]

1 | THE IMPACT OF HYPERTENSION ON NEUROCOGNITIVE FUNCTIONING

The location of a brain lesion is one of the most important factors influencing the cognitive deficit after stroke. However, the evidence that similar lesions in similar locations may result in different outcomes suggests that other variables may also play a role. Vulnerability factors can affect the compensatory brain network integration that follows the disconnection of cerebral regions induced by stroke.[10] Underlying vulnerabilities include blood-brain barrier disruption, small vessel disease, and amyloid pathology.[10] In this regard, hypertension plays a crucial role.

Cerebral vasculature is indeed the prime target of the harmful effects of hypertension. Chronic hypertension is well known to affect the structure and function of cerebral blood vessels.[11] Remodeling and stiffening of the vascular wall derive from interacting mechanical, cellular, and molecular factors that alter its structure and composition.[12,13] These changes are primarily intended to protect downstream microvasculature from the mechanical stress induced by the increase in transmural pressure.[11] Over time, however, they result in maladaptive responses that lead to vascular and perivascular dysfunction and damage.[11] Arterial stiffening may reduce resting cerebral blood flow and deplete cerebrovascular reserve.[11,14] Neurovascular uncoupling may compromise substrate delivery and make the brain more vulnerable to vascular insufficiency.[11] The increase in blood-brain barrier permeability favored by vascular oxidative stress and inflammation associated with hypertension may result in water shift

and local edema leading to microvascular compression and impairment of oligodendrocyte development and function.[15,16] Hypoxia-ischemia and impaired remyelination are additional contributors to white matter damage. The vascular and perivascular dysfunction resulting from different stages of chronic hypertension can impair the clearance of waste products such as amyloid-β, leading to its accumulation.[17] The loss of nitric oxide and prostacyclin bioavailability may increase amyloid-β formation because of increased processing of amyloid precursor protein (APP) by secretase enzymes.[11] Importantly, interactions between all these different pathogenic mechanisms amplify the deleterious impact of hypertension and contribute to the development of brain atrophy. Microinfarcts and microbleeds also disrupt brain connectivity and reduce network efficiency.[18] More recently, blood pressure variability has also been recognized to be responsible for alterations in brain structure and function,[19–21] and a risk factor of faster cognitive decline in ischemic stroke patients.[22] It is hypothesized that hemodynamic instability, up-regulation of the neuro-inflammatory milieu, and reactive gliosis are hypothesized to be the putative mechanisms.[23]

2 | WHEN COGNITIVE IMPAIRMENT HAS A VASCULAR ORIGIN: THE ROLE OF PREVENTION

Poststroke cognitive impairment may be the direct consequence of the vascular lesion, which is the most likely cause in patients with normal cognitive functioning before a strategic infarct.[24] In many cases, however, cognitive impairment may be the consequence of the additive effect of the acute cerebrovascular lesion and pre-existing changes due to aging and comorbidities.[25] Associated cerebral vulnerabilities may increase the effect of stroke on brain functioning and compensatory networking, and their summation may reach the threshold of lesions required to induce cognitive deficits.[24]

The notion of potentially treatable, cumulative mechanisms points out the opportunity to develop strategies to preserve cerebral functions poststroke. Although the clinical determinants of poststroke cognitive impairment are not fully understood, putative risk factors have been reported, including smoking, hypertension, diabetes mellitus, atrial fibrillation, and carotid atherosclerosis.[26–29] Of note, appropriate vascular risk management after stroke has been shown to decrease the risk of stroke recurrence and cognitive impairment in the longitudinal data analysis of 4413 patients from the community-based South London Stroke Register.[30]

In summary, understanding the pathogenesis of cognitive impairment after stroke is fundamental to reducing its global burden. Controlling vascular risk factors represents an important strategy to prevent or delay the onset of cognitive deterioration among stroke survivors. Differences in and overlaps of comorbidities are common among stroke patients, and individualized interventions are needed to address this variability in clinical practice.

CONFLICT OF INTEREST

The authors have no competing interests.

ORCID

Simona Lattanzi MD, PhD https://orcid.org/0000-0001-8748-0083

REFERENCES

1. Zuo L, Dong Y, Liao X, et al. Risk factors for decline in Montreal cognitive assessment (moca) scores in patients with acute transient ischemic attack and minor stroke. *J Clin Hypertens*. 2022.
2. Verdelho A, Wardlaw J, Pavlovic A, et al. Cognitive impairment in patients with cerebrovascular disease: a white paper from the links between stroke ESO Dementia Committee. *Eur Stroke J*. 2021;6:5-17.
3. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol*. 2009;8:1006-1018.
4. Tatemichi TK, Desmond DW, Mayeux R, et al. Dementia after stroke: baseline frequency, risks, and clinical features in a hospitalized cohort. *Neurology*. 1992;42:1185-1193.
5. Nys GMS, Van Zandvoort MJE, De Kort PLM, Van Der Worp HB, et al. The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. *Neurology*. 2005;64:821-827.
6. Nys GMS, Van Zandvoort MJE, Van Der Worp HB, et al. Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke. *J Neurol Sci*. 2006;247:149-156.
7. Edwards JD, Kapoor A, Linkewich E, Swartz RH. Return to work after young stroke: a systematic review. *Int J Stroke*. 2018;13:243-256.
8. Pollock A, St George B, Fenton M, Firkins L. Top 10 research priorities relating to life after stroke–consensus from stroke survivors, caregivers, and health professionals. *Int J Stroke*. 2014;9:313-320.
9. Lattanzi S, Coccia M, Pulcini A, et al. Endovascular treatment and cognitive outcome after anterior circulation ischemic stroke. *Sci Rep*. 2020;10:18524.
10. Lim J-S, Lee J-J, Woo C-W. Post-Stroke Cognitive impairment: pathophysiological insights into brain disconnectome from advanced neuroimaging analysis techniques. *J Stroke*. 2021;23:297-311.
11. Iadecola C, Gottesman RF. Neurovascular and cognitive dysfunction in hypertension. *Circ Res*. 2019;124:1025-1044.
12. Iulita MF, Noriega De La Colina A, Girouard H. Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? *J Neurochem*. 2018;144:527-548.
13. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. *J Exp Med*. 2018;215:21-33.
14. Dubose LE, Boles Ponto LL, Moser DJ, Harlynn E, Reierson L, Pierce GL. Higher aortic stiffness is associated with lower global cerebrovascular reserve among older humans. *Hypertension*. 2018;72:476-482.
15. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease–systematic review and meta-analysis. *Neurobiol Aging*. 2009;30:337-352.
16. Maclullich AMJ, Ferguson KJ, Reid LM, et al. Higher systolic blood pressure is associated with increased water diffusivity in normal-appearing white matter. *Stroke*. 2009;40:3869-3871.
17. Tarasoff-Conway JM, Carare RO, Osorio RS, et al. Clearance systems in the brain-implications for Alzheimer disease. *Nat Rev Neurol*. 2015;11:457-470.
18. Iadecola C. The pathobiology of vascular dementia. *Neuron*. 2013;80:844-866.
19. Tully PJ, Yano Y, Launer LJ, et al. Association between blood pressure variability and cerebral small-vessel disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2020;9:e013841.
20. De Heus RAA, Tzourio C, Lee EJoL, et al, VARIABLE BRAIN Consortium. Association between blood pressure variability with dementia and cognitive impairment: a systematic review and meta-analysis. *Hypertension*. 2021;78:1478-1489.
21. Lattanzi S, Silvestrini M. Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. *Neurology*. 2015;85:557-558.

22. Kim Y, Lim J-S, Oh MiS, et al. Blood pressure variability is related to faster cognitive decline in ischemic stroke patients: PICASSO subanalysis. *Sci Rep*. 2021;11:5049.
23. Lattanzi S, Vernieri F, Silvestrini M. Blood pressure variability and neurocognitive functioning. *J Clin Hypertens (Greenwich)*. 2018;20:645-647.
24. Pasquier F, Leys D. Why are stroke patients prone to develop dementia? *J Neurol*. 1997;244:135-142.
25. Hennerici MG. What are the mechanisms for post-stroke dementia? *Lancet Neurol*. 2009;8:973-975.
26. Lo JW, Crawford JD, Desmond DW, et al. Stroke and Cognition (STROKOG) Collaboration. Profile of and risk factors for poststroke cognitive impairment in diverse ethnoregional groups. *Neurology*. 2019;93:e2257-2271.
27. Obaid M, Douiri A, Flach C, Prasad V, Marshall I. Can we prevent post-stroke cognitive impairment? An umbrella review of risk factors and treatments. *BMJ Open*. 2020;10:e037982.
28. Lattanzi S, Carbonari L, Pagliariccio G, et al. Neurocognitive functioning and cerebrovascular reactivity after carotid endarterectomy. *Neurology*. 2018;90:e307-315.
29. Lattanzi S, Carbonari L, Pagliariccio G, et al. Predictors of cognitive functioning after carotid revascularization. *J Neurol Sci*. 2019;405:116435.
30. Douiri A, Mckevitt C, Emmett ES, Rudd AG, Wolfe CDA. Long-term effects of secondary prevention on cognitive function in stroke patients. *Circulation*. 2013;128:1341-1348.

How to cite this article: Lattanzi S, Divani AA, Brigo F. When cognitive impairment has a vascular origin. *J Clin Hypertens*. 2022;24:858–860. https://doi.org/10.1111/jch.14452