Brain atrophy, N-terminal brain natriuretic peptide and carotid disease: interconnecting relationships between cerebral perfusion, cardiovascular disease, inflammation and cognitive decline.

Sarah T Pendlebury FRCP DPhil, Peter M Rothwell FRCP MD PhD FMed Sci

Stroke Prevention Research Unit, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, and the University of Oxford, UK

Oxford NIHR Biomedical Research Centre, John Radcliffe Hospital, Oxford, UK

Correspondence to:

Associate Professor Sarah Pendlebury
Stroke Prevention Research Unit
Nuffield Department of Clinical Neurosciences
Level 6 West Wing
John Radcliffe Hospital
Oxford OX3 9DU
Tel: +44 1865 231603
Fax: +44 1865 234639

Email: sarah.pendlebury@ndcn.ox.ac.uk

Invited editorial, Tracking number ATVB/2016/308362.

In this issue, Sabayan et al discuss their findings from the AGES-Reykjavik study, on the association between brain atrophy and baseline N-terminal brain natriuretic peptide (NT-proBNP), a marker of cardiac dysfunction and carotid intima media thickness (CIMT), a marker of carotid atherosclerosis burden.[1] They found that both higher NT-proBNP and CIMT were associated with longer term decline in total brain and grey matter volume but not with white matter volume. The highest rates of brain volume decline (at around three times that seen in normal ageing) were seen in subjects with both high NT-proBNP and CIMT and this was independent of age, education and cardiovascular factors.

Strengths of the study include the longitudinal population (volunteer) design with brain volumes measured both at baseline and after 5 years and the determination of both cardiac and carotid markers in the same large sample. The authors acknowledge the possibility that selection bias may have occurred in that only those who were MRI-safe and willing and who returned for 5-year MRI were included[2] which cannot be corrected by statistical methods. Also, although adjustment for hypertension was made, there was no measurement of blood pressure variability, a proxy for vessel stiffness which may be important in driving atherosclerosis and may cause elevation in NT-proBNP through increasing cardiac workload.[3] Previous studies have shown that brain atrophy and cognitive impairment are associated with cardiac failure[4] and symptomatic coronary vascular disease,[5] and both symptomatic and asymptomatic carotid stenosis although not all have found relationships with CIMT.[6] The current study is important in showing the prognostic value of baseline markers of cardiac and carotid disease in a community based sample in which rates of symptomatic vascular disease were low (18.5% coronary heart disease, 4.6% stroke).

The authors discuss possible mechanisms for the observed associations between brain atrophy and cardiac and carotid disease. The relationship between cerebral perfusion and brain health is well established: low cardiac output results in selective neuronal death and brain atrophy and low cerebral perfusion has been implicated in the development of white matter disease and neurodegeneration. Although autoregulation acts to maintain a constant cerebral blood flow, this may be challenged by sudden change in systemic pressure, end stage cardiac failure or by severe extra or intra-cranial atherosclerosis. However, it is unlikely that cardiac dysfunction and or carotid disease severe enough to impact on cerebral perfusion can explain all the observed associations in this study of community dwelling volunteer subjects. Rates of symptomatic vascular disease were low and associations remained after exclusion of those with previous stroke. As stated by the authors, high NT-proBNP and CIMT might reflect a global systemic vascular condition affecting the small as well as larger vessels. Indeed, higher NT-proBNP levels have been shown to associate with

retinal microvascular disease[7] and with subcortical vascular dementia.[8] The lack of a relationship between white matter volume loss and NT-proBNP /CIMT in the current study is therefore perhaps unexpected but small vessel disease damage might have been better detected using more sensitive MR measures of white matter lesion load or white matter tract disruption. Genetic factors may mediate some of the shared susceptibility to cardiovascular disease and cognitive decline: genetic polymorphisms have recently been shown to increase the risk of both vascular disease (stroke) and Alzheimer's dementia.[9] Also, reverse causation may play a role in increasing NT-proBNP levels through loss of neurohumeral and physiological (eg blood pressure) homeostasis caused by the failing brain.

Associations between brain atrophy and NT-proBNP and CIMT might also be mediated by inflammatory processes: reciprocal relationships exist between cardiac disease, atherosclerosis, blood pressure variability and inflammation.[3] In addition, although NT-proBNP is characteristically associated with cardiac dysfunction, high levels are also seen in pro-inflammatory conditions including acute arthritis, cancer, renal failure and sepsis in which it is an independent predictor of mortality.[10] Inflammatory mediators influence brain microglia possibly potentiating neurodegeneration and blood brain barrier dysfunction[11] and NT-proBNP levels are predictive of cognitive decline in healthy individuals independent of vascular or Alzheimer risk factors.[12] Systemic inflammation linked to ageing, obesity, diabetes mellitus and hypertension has been implicated in coronary microvascular endothelial inflammation, diastolic dysfunction and heart failure with preserved ejection fraction.[13]

Future studies should aim to determine the mechanisms underlying the link between brain atrophy, markers of cardiac dysfunction and carotid atherosclerotic disease including the role of cerebral perfusion, inflammation and the systemic milieu, microvascular pathology, the nature of cardiac dysfunction and the underlying causes of NT-proBNP elevation.

References

1. Sabayan B, Buchem MA, Sigurdsson S, Zhang Q, Meirelles O, Harris T, Gudnason V, Arai A, Launer L. Cardiac and carotid markers link with accelerated brain atrophy: The AGES-Reykjavik Study. Arteriosclerosis, Thrombosis and Vascular Biology. 2016;xxxx

2. Pendlebury ST, Chen PJ, Welch SJ, et al; Oxford Vascular Study. Methodological Factors in Determining Risk of Dementia After Transient Ischemic Attack and Stroke: (II) Effect of Attrition on Follow-Up. Stroke. 2015;46:1494-500.

3. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet. 2010;375:938-48.

4. Alagiakrishnan K, Mah D, Ahmed A, Ezekowitz J. Cognitive decline in heart failure. Heart Fail Rev. 2016 Jun 14. [Epub ahead of print]

5.Volonghi I, Pendlebury ST, Welch SJ, Mehta Z, Rothwell PM. Cognitive outcomes after acute coronary syndrome: a population based comparison with transient ischaemic attack and minor stroke. Heart. 2013;99:1509-14.

6. Muller M, van der Graaf Y, Algra A, Hendrikse J, Mali WP, Geerlings MI; SMART Study Group. Carotid atherosclerosis and progression of brain atrophy: the SMART-MR study. Ann Neurol. 2011;70:237-44.

7. Mutlu U, Ikram MA, Hofman A, de Jong PT, Klaver CC, Ikram MK. N-Terminal Pro-B-Type Natriuretic Peptide Is Related to Retinal Microvascular Damage: The Rotterdam Study. Arterioscler Thromb Vasc Biol. 2016;36:1698-702.

8. Kondziella D, Göthlin M, Fu M, Zetterberg H, Wallin A. B-type natriuretic peptide plasma levels are elevated in subcortical vascular dementia. Neuroreport. 2009;20:825-7.

9. Traylor M, Adib-Samii P, Harold D; Alzheimer's Disease Neuroimaging Initiative; International Stroke Genetics Consortium (ISGC), UK Young Lacunar Stroke DNA resource, Dichgans M, Williams J, Lewis CM, Markus HS; METASTROKE; International Genomics of Alzheimer's Project (IGAP), investigators. Shared genetic contribution to Ischaemic Stroke and Alzheimer's Disease. Ann Neurol.

2016 Feb 23. doi: 10.1002/ana.24621. [Epub ahead of print]

10. Wang F, Wu Y, Tang L, et al. Brain natriuretic peptide for prediction of mortality in patients with sepsis: a systematic review and meta-analysis. Crit Care. 2012;16:R74.

11. Le Thuc O, Blondeau N, Nahon JL, Rovère C. The complex contribution of chemokines to neuroinflammation: switching from beneficial to detrimental effects. Ann N Y Acad Sci. 2015;1351:127-40.

12. Cushman M, Callas PW, McClure LA, et al. N-Terminal Pro-B-Type Natriuretic Peptide and Risk of Future Cognitive Impairment in the REGARDS Cohort. J Alzheimers Dis. 2016;54:497-503

13. Glezeva N, Baugh JA. Role of inflammation in the pathogenesis of heart failure with preserved ejection fraction and its potential as a therapeutic target. Heart Fail Rev. 2014;19:681-94.