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RESEARCH ARTICLE

Small Vessel Cerebrovascular Pathology is a Major Feature in the Pathogenesis of Alzheimer's Disease or Age-Related Dementia

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ABSTRACT

Historically, cerebrovascular abnormalities were recognized as prominent in the pathology of age-related dementia. In more recent decades, however, research and funding for development of therapeutics has almost entirely been focused on β-amyloid and tau deposits (as described by Alzheimer in pre-senile dementia), despite a lack of conclusive evidence of a causal relationship or efficacy of targeted treatment on cognitive decline or dementia. Here we present a brief history of the evidence for a dominant vascular component of Alzheimer's Disease and highlight a potential target for slowing the functional progression of the disease.

Background:

Over the past few decades, the biological definition of, and development of therapeutics for, Alzheimer's disease (AD) have focused on β-amyloid plaques and neurofibrillary tau deposits [1]. Despite promising pre-clinical data, all clinical studies attempting to use antibodies to eliminate amyloid plaques have failed at various stages or have demonstrated very low efficacy for their primary targeted outcome – cognitive impairment. Even the 2018 National Institute on Aging – Alzheimer's Association (NIA-AA) research framework for AD concedes that β-amyloid deposition and pathologic tau may not be causal of AD pathogenesis and may exist without cognitive impairment [1].

Cerebrovascular pathology is prevalent in Alzheimer's:

While AD and vascular dementia (VD) are currently considered as distinct diagnoses, cerebrovascular pathology is prominent in patients diagnosed with AD [2-6], and occurs early in the progress of dementia [4,7]. Studies have shown that the presence of small vessel infarcts [2] and the occurrence of stroke [8] amplify the severity of functional impairment and the progression of the disease. AD and cerebrovascular disease share common risk factors such as hypertension [9,10], atherosclerosis [9,10], atrial fibrillation[11], diabetes [9,12], and elevated homocysteine blood concentrations [9], and we and others have argued that AD pathology is initiated through microvascular abnormalities [5-7,13]. Regardless of whether cerebrovascular pathology is causal of AD, it is becoming increasingly clear that vascular factors should be a target for slowing dementia progression, especially since effective preventative therapeutics already exist.

In this brief review we focus on the cerebrovascular factors that are associated with cognitive decline and dementia. The history of the recognition of that association goes back over 100 years with early works by Emil Kraepelin [14] and his junior colleague Alois Alzheimer [15] describing arteriosclerosis and strangulation of blood supply to the brain in "senile dementia". Interestingly, Alzheimer's now-famous description of a 51-year-old patient with cortical atrophy and minimal cerebral atherosclerosis [16] was included in the 8th edition of Kraepelin's textbook *Psychiatrie* as a "pre-senile" dementia. It was not until a half century later that the Alzheimer name was applied to age-related or late-onset dementia [17]. In that process, underlying vascular factors were somewhat marginalized in the rush to find control of metabolic causes of amyloid deposition.

Cerebrovascular findings are strongly associated with cognitive decline in Alzheimer's:

Cerebrovascular histopathology is prominent in AD, with 30% having concomitant infarcts and nearly all exhibiting periventricular white matter lesions, microvascular degeneration, and/or cerebral amyloid angiopathy [7]. The Nun's study, reported by David Snowdon and his colleagues [2] refocused attention on the importance of cerebrovascular findings on the clinical manifestation of AD. Of those participants who met the post-mortem criteria for AD, adjusting for the number of β-amyloid plaques and neurofibrillary tangles, those with co-existing lacunar infarcts were 20 times more likely to meet the clinical criteria for dementia prior to death. The Oxford Project to Investigate Memory and Ageing (OPTIMA) study [18] similarly showed that the presence of cerebrovascular disease was a determinant of poorer cognitive function early in AD. More recent studies utilizing *in vivo* imaging techniques, such magnetic resonance imaging, have confirmed the prominence of cerebrovascular findings in AD and related dementias, and the relationship with cognitive function and decline [13,19-21]. The clinical significance of vascular contributions to cognitive impairment and dementia, and the need to give more focus on them in clinical practice, has been highlighted by the American Heart Association/American Stroke Association and recognized by the Alzheimer's Association and American Academy of Neurology [22] and followed up by the critique of the NIA-AA framework in the recent publication by a working group of prominent investigators in the field [4].

The relationship between vascular risk factors and AD and related dementias is increasingly recognized, and the utility of treating hypertension, diabetes, and atrial fibrillation as a preventative measure is becoming clearer [23]. A recent systematic review and meta-analysis on evidence-based prevention of Alzheimer's disease [24] has also identified hyperhomocysteinaemia as a promising modifiable risk factor to target, with Class I, Level A2 strength of evidence. Other meta-analyses [25,26] and narrative reviews [27] have had similar findings.

Hyperhomocysteinemia may underly cerebrovascular pathology:

The recognition of the importance of elevated homocysteine on vascular factors and

cognitive impairment originated in the study of homocystinuria, a genetic condition in children that results in very high levels of homocysteine, thromboembolic changes in blood vessels, disrupted microvascular histology, and abnormalities in brain function [28,29]. This association of vascular pathology with homocysteine was emphasized later in the Framingham study [30] which showed that the degree of carotid artery narrowing measured on ultrasound had a clear relationship with plasma homocysteine level. In the same study, the highest quartile of plasma homocysteine concentration was associated with nearly a two-fold increase in the risk of stroke [31] and a higher incidence of dementia [32]. In our Nutrition and Memory in the Elderly (NAME) study [13], high plasma homocysteine was associated with cerebrovascular disease, and showed a dose-response relationship with brain atrophy and cognitive impairment in those with small vessel disease. Other studies have also reported a relationship between homocysteine and cerebrovascular small vessel disease [19,33] and cognitive impairment [34-36]. Elevated homocysteine in the blood can result from several factors, including renal functional and lifestyle behaviors [27], however it is often a marker for low B-vitamin status (folate, B12 and B6). A number of clinical trials employing B-vitamin supplementation to lower homocysteine and prevent cognitive decline have had positive results [37-39]. The commonalities behind these trials are that the participants had low B vitamin status and were either at-risk or in early stages of cognitive decline (but not moderately or severely demented). The studies with null findings or showing minimal benefits of B-vitamins were limited by patient selection with only low or moderate elevations of homocysteine.

Cerebrovascular pathology likely mediates the effect of hyperhomocysteinemia on cognitive decline:

Cerebrovascular pathology, as a part of Vascular Dementia, Mixed Dementia, and Alzheimer's dementia with vascular pathology, is responsible for at least half of cases of cognitive decline [4,40]. The recent response to the NIA-AA Research Framework that biologically defined AD solely on β-amyloid plaques and neurofibrillary tau deposits strongly recommended including biomarkers of cerebrovascular disease in the framework and definition [4]

Conclusions and recommendations:

Given the expense of β-amyloid antibody therapies and their lack of efficacy for cognitive outcomes, it makes sense to consider cost-effective strategies for preventing and/or delaying the onset of dementia. From a public health and clinical medicine perspective, more attention needs to be directed toward aggressive treatment of vascular risk factors for age-related cognitive decline and dementia, including management of hypertension, arrhythmias, and diabetes. Based on the strength of evidence, physicians should consider adding homocysteine and B vitamin status as variables to consider as targets for maintaining their patients' cognitive health and cerebrovascular integrity. Measurement of blood homocysteine, and correction when elevated, should become a routine part of clinical care of aging patients.

Conflicts of Interest Statement: The authors have no conflicts of interest to declare.

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References:

1. Jack Jr CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*. 2018;14(4):535-562.
2. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA*. Mar 12 1997;277(10):813-7.
3. Toledo JB, Arnold SE, Raible K, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*. 2013;136(9):2697-2706.
4. Sweeney MD, Montagne A, Sagare AP, et al. Vascular dysfunction—the disregarded partner of Alzheimer's disease. *Alzheimer's & Dementia*. 2019;15(1):158-167.
5. Klohs J. An integrated view on vascular dysfunction in Alzheimer's disease. *Neurodegenerative Diseases*. 2019;19(3-4):109-127.
6. Govindpani K, McNamara LG, Smith NR, et al. Vascular dysfunction in Alzheimer's disease: a prelude to the pathological process or a consequence of it? *Journal of clinical medicine*. 2019;8(5):651.
7. De la Torre J. Alzheimer disease as a vascular disorder: nosological evidence. *Stroke*. 2002;33(4):1152-1162.
8. Pasquier F, Leys D, Scheltens P. The influence of coincidental vascular pathology on symptomatology and course of Alzheimer's disease. *Alzheimer's disease—From basic research to clinical applications*. 1998:117-127.
9. Breteler MM. Vascular risk factors for Alzheimer's disease:: An epidemiologic perspective. *Neurobiology of aging*. 2000;21(2):153-160.
10. Breteler MM. Vascular involvement in cognitive decline and dementia: epidemiologic evidence from the Rotterdam Study and the Rotterdam Scan Study. *Annals of the New York Academy of Sciences*. 2000;903(1):457-465.
11. Ott A, Breteler MM, De Bruyne MC, Van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study: the Rotterdam Study. *Stroke*. 1997;28(2):316-321.
12. Ott A, Stolk R, Hofman A, van Harskamp F, Grobbee D, Breteler M. Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia*. 1996;39(11):1392-1397.
13. Scott TM, Bhadelia RA, Qiu WQ, Folstein MF, Rosenberg IH. Small Vessel Cerebrovascular Pathology Identified by Magnetic Resonance Imaging Is Prevalent in Alzheimer's Disease and Mild Cognitive Impairment: A Potential Target for Intervention. *J Alzheimers Dis*. 2018;65(1):293-302. doi:10.3233/JAD-180366
14. Kraepelin E. Das arteriosklerotische Irresein. *Psychiatrie Ein Lehrbuch für Studierende und Ärzte*. 1910;2:554-593.
15. Alzheimer A. Neuere Arbeiten über die Dementia senilis und die auf atheromatöser Gefässerkrankung basierenden Gehirnkrankheiten. *European Neurology*. 1898;3(1):101-115.
16. Alzheimer A. Uber eine eigenartige Erkrankung der Hirnrinde. *Zentralbl Nervenh Psych*. 1907 1907;18:177-179.
17. Knopman DS, Petersen RC, Jack CR. A brief history of "Alzheimer disease": Multiple meanings separated by a common name. *Neurology*. 2019;92(22):1053-1059.
18. Esiri MM, Joachim C, Sloan C, et al. Cerebral subcortical small vessel disease in subjects with pathologically confirmed Alzheimer disease: a clinicopathologic study in the Oxford Project to Investigate Memory and Ageing (OPTIMA). *Alzheimer Dis Assoc Disord*. Jan-Mar 2014;28(1):30-5. doi:10.1097/WAD.0b013e31829b72f1
19. Vermeer SE, Van Dijk EJ, Koudstaal PJ, et al. Homocysteine, silent brain infarcts, and white matter lesions: The Rotterdam Scan Study. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*. 2002;51(3):285-289.
20. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke*. 2008;39(10):2712-2719.
21. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *New England Journal of Medicine*. 2003;348(13):1215-1222.
22. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. Sep 2011;42(9):2672-713. doi:10.1161/STR.0b013e3182299496
23. de Leeuw F-E, Kalaria R, Scheltens P. Treatment of vascular risk factors to delay Alzheimer's disease? In: Gauthier S, Scheltens P, Cummings J, eds. *Alzheimer's Disease and Related Disorders*. Informa Healthcare; 2005:153.

24. Yu JT, Xu W, Tan CC, et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry*. Nov 2020;91(11):1201-1209. doi:10.1136/jnnp-2019-321913

25. Wang Z, Zhu W, Xing Y, Jia J, Tang Y. B vitamins and prevention of cognitive decline and incident dementia: a systematic review and meta-analysis. *Nutr Rev*. Aug 25 2021;doi:10.1093/nutrit/nuab057

26. Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC public health*. 2014;14(1):1-33.

27. Smith A, Refsum H. Homocysteine–from disease biomarker to disease prevention. *Journal of Internal Medicine*. 2021;290(4):826-854.

28. Carson NA, Neill D. Metabolic abnormalities detected in a survey of mentally backward individuals in Northern Ireland. *Archives of disease in childhood*. 1962;37(195):505.

29. McCully K. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *The American journal of pathology*. 1969;56(1):111.

30. Selhub J, Jacques PF, Bostom AG, et al. Relationship between plasma homocysteine, vitamin status and extracranial carotid-artery stenosis in the Framingham Study population. *The Journal of nutrition*. 1996;126(suppl_4):1258S-1265S.

31. Bostom AG, Rosenberg IH, Silbershatz H, et al. Nonfasting plasma total homocysteine levels and stroke incidence in elderly persons: the Framingham Study. *Annals of internal medicine*. 1999;131(5):352-355.

32. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *New England journal of medicine*. 2002;346(7):476-483.

33. Teng Z, Feng J, Liu R, et al. Cerebral small vessel disease mediates the association between homocysteine and cognitive function. *Frontiers in Aging Neuroscience*. 2022;14

34. Riggs KM, Spiro A, 3rd, Tucker K, Rush D. Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study. *Am J Clin Nutr*. Mar 1996;63(3):306-14. doi:10.1093/ajcn/63.3.306

35. Tucker KL, Qiao N, Scott T, Rosenberg I, Spiro A, 3rd. High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. *Am J Clin Nutr*. Sep 2005;82(3):627-35. doi:10.1093/ajcn.82.3.627

36. Kado DM, Karlamangla AS, Huang M-H, et al. Homocysteine versus the vitamins folate, B6, and B12 as predictors of cognitive function and decline in older high-functioning adults: MacArthur Studies of Successful Aging. *The American journal of medicine*. 2005;118(2):161-167.

37. de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. *International journal of geriatric psychiatry*. 2012;27(6):592-600.

38. Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *Lancet*. Jan 20 2007;369(9557):208-16. doi:10.1016/S0140-6736(07)60109-3

39. Scott TM, Rogers G, Weiner DE, et al. B-Vitamin Therapy for Kidney Transplant Recipients Lowers Homocysteine and Improves Selective Cognitive Outcomes in the Randomized FAVORIT Ancillary Cognitive Trial. *J Prev Alzheimers Dis*. 2017;4(3):174-182. doi:10.14283/jpad.2017.15

40. Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. *Alzheimer disease and associated disorders*. 1999;