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Vascular Disease and Cognitive Impairment

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Vascular disease seems to be important in cognitive impairment and dementia in the elderly. The entities implicated comprise various vascular risk factors and cerebrovascular disease including large cortical infarcts, single strategically-placed or multiple small infarcts, cerebral hemorrhage, cortical changes due to hypoperfusion (eg, hippocampal sclerosis, ischemic-anoxic damage, cortical laminar sclerosis), white matter changes, and a variety of vasculopathies (eg, lipohyalinosis, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral amyloid angiopathy). The traditional view is that the two most common causes of dementia are vascular dementia and Alzheimer's disease. While there is general agreement that vascular dementia is caused by cerebrovascular disease and its risk factors, their contribution to what we define clinically as Alzheimer's disease, theoretically characterized by the deposition of amyloid beta, is less clear. More recently, the concept of vascular cognitive impairment has been coined as an umbrella term that encompasses all instances of cognitive impairment due to vascular risk factors and cerebrovascular disease, including vascular dementia, and Alzheimer's disease with a vascular contribution.[1] As our understanding grows, new questions arise: does cerebrovascular disease, including white matter lesions and silent infarcts, lead to a specific pattern of cognitive impairment, and if so, how? Does cerebrovascular disease lead to a dementia syndrome indistinguishable from Alzheimer's disease? What are the molecular mechanisms underlying the associations between the various vascular risk factors and cognitive impairment? Do changes in the microvasculature lead to the development of Alzheimer pathology?

Leys et al.[2] summarized previous studies that explored the impact of clinical stroke on the risk of post-stroke dementia (PSD). Accordingly, stroke increases the risk of dementia, with a prevalence ranging from 13.6 to 32% within 3 months to 1 year after stroke, and after stroke

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incidence rates of new onset dementia range from 24% within 3 years to 33.3% within 5 years.[2] The impact of stroke on dementia risk seems to be independent of pre-stroke cognitive function.[3] Mechanisms through which stroke could lead to cognitive impairment include destruction of brain parenchyma with atrophy,[4, 5] damage in strategic locations that lead to amnestic syndromes, such as thalamic strokes,[6] or an increase in the deposition of amyloid β protein. Stroke could also decrease the threshold of Alzheimer's disease pathology for the manifestation of dementia[7] implying that stroke and Alzheimer's disease have an additive effect on dementia. Recent evidence suggests that overexpression of p25 and cyclin dependent kinase 5(cdk5) lead to increased levels of BACE1 mRNA and protein, which in turn is correlated with amyloidogenic processing.[8] Increased production of p25 and enhancement of cdk5 activity has been shown to occur in rodent models of ischemia and hypoxia due to hypoperfusion.[9]

The effect of silent infarcts and CT- and MRI-detected white matter changes on cognition is more controversial. These vascular lesions are seen in healthy individuals with intact cognitive function, and it is questioned whether they play a role in cognitive decline in the elderly.[10] On the other hand, the results of many clinical, epidemiological, and pathological studies suggest that people with these types of white matter changes and silent infarcts are more likely to develop cognitive impairment and dementia,[11, 12] and that the extent and location of the white matter changes determine the neuropsychological profile.[13-15] The mechanisms through which these small-vessel pathologies lead to cognitive decline are unclear, but one putative mechanism is the disconnection of cortical-subcortical -possibly cholinergic- pathways.[16, 17] The thalamus is a key component in these pathways, not only of frontal-subcortical circuits but also of temporo-limbic circuits important for memory storage and retrieval. Thalamic changes due to local lesions or subcortical diaschisis lead to lower performance on multiple cognitive behaviors associated with frontal and temporal lobe function.[13, 18]

Vascular risk factors including diabetes,[19-22] insulin resistance,[23] hypertension,[24] heart disease,[25] smoking,[26, 27] and obesity,[28] are each independently associated with an increased risk of cognitive impairment and dementia and are frequent in the elderly. The associations between vascular risk factors and dementia may depend on the stage of the lifespan in which they are examined. For example, high blood pressure and obesity in middle-age have been found as risk factors for dementia in old age.[29, 30] In old age, however, these associations seem to be attenuated or inverse for reasons that are uncertain.[31-33]

Although these vascular factors may increase dementia risk through cerebral small or large-vessel disease, they may also act through non-cerebrovascular mechanisms. Diabetes can directly affect amyloid accumulation in the brain.[34] Hyperinsulinemia, which either precedes or accompanies diabetes,[35] disrupts brain amyloid β clearance by competing for the insulin degrading enzyme.[36] In addition receptors for advanced glycosilation products, which have been identified immunohistochemically in senile plaques and neurofibrillary tangles have been shown to be specific cell surface receptors for amyloid β, and glycation of amyloid β enhances its aggregation in vitro.[37] Hypertension is also associated with increased vascular permeability with protein extravasation,[38] leading in turn to chronic edema and tissue necrosis.[38] Dysfunction of the blood-brain barrier can induce penetration of substances from the blood into the brain tissue, where they may interact with neuronal or synaptic function or influence accumulation of amyloid β leading to cognitive impairment.[39] Recent evidence also indicates that in obese persons adipose tissue is active producing adipokines critical in metabolism, and cytokines important in inflammation Adiponectin,[40] leptin,[41] resistin,[41] tumor necrosis factor-α and interleukin-6, are also produced and correlate with insulin resistance and hyperinsulinemia. Whether peripherally secreted adipokines and cytokines are directly related to Alzheimer's disease or whether they are only markers of insulin resistance and hyperinsulinemia is unclear.

It is possible that vascular risk factors and cerebrovascular disease are not causal but rather concomitant diseases frequent in the elderly with dementia. It is important to clarify whether they in fact affect cognition in old age, and -if yes- how. While the incidence of cardiovascular disease and stroke is decreasing due to better preventive and treatment measures (e.g. treatment of hypertension and dyslipidemia, aspirin), their absolute burden is increasing because of increasing life span. In contrast, obesity, insulin resistance, and type II diabetes are increasing in frequency in the developed and developing world. If the products of adipose tissue, high insulin and glucose levels, and their products have a direct effect on cognitive impairment in addition to those mediated by cerebrovascular disease, the public health impact could be devastating. We estimated that in New York City the presence of diabetes or hyperinsulinemia in elderly people could account for 39% of cases of Alzheimer's disease.[42] The implication of vascular disease as a causal factor in dementia is that a large proportion of dementia cases could be preventable or treatable. There have been no investigations examining how strategies used to treat cardio- and cerebrovascular disorder might also affect cognition.

Lifestyle intervention and drugs like metformin can decrease hyperinsulinemia and the risk of diabetes, and it is possible that these interventions might also decrease the risk of cognitive impairment. Rosiglitazone treatment of diabetes shows promise in the treatment of Alzheimer's disease,[43] although concerns about its safety may limit this drug's usefulness.[44] The four randomized, placebo-controlled studies that investigated the effects of antihypertensive agents on the incidence of dementia (Systolic Hypertension in Europe (Syst-Eur) study, Study on Cognition and Prognosis in the Elderly (SCOPE), Systolic Hypertension in the Elderly Program (SHEP), and Perindopril Protection Against Recurrent Stroke Study (PROGRESS)) produced inconsistent results. In the Syst-Eur study[45, 46] active treatment with nitrendipine, enalapril, and/or hydrochlorothiazide reduced the rate of dementia by 50% compared with placebo ($p=0.05$). In the PROGRESS study[47] treatment with perindopril and indapamide was associated with reduced cognitive decline (risk ratio 19%, $p=0.01$), but the SCOPE[48] (candesartan or hydrochlorothiazide vs placebo) and SHEP trial (chlorthalidone, atenolol, or reserpine vs placebo) found no significant difference between the active treatment and placebo on the incidence of dementia. In the SHEP trial, however, this may have been caused by differential drop out of study participants.[49] Knowing that the association between blood pressure and cognitive impairment seems to depend on the age of the patient and the stage of the disease process as described above, it seems reasonable that the findings of hypertension treatment trials differ between study populations with different age distributions and pathology burdens. Also, it has been suggested that the effect of antihypertensive medication on cognition differs between drug classes with possibly the strongest effect for calcium channel blockers and ACE inhibitors. The effects of drugs currently used to treat Alzheimer's disease are modest. A meta-analysis concluded that the benefits were of uncertain clinical meaningfulness with any of the approved cholinesterase inhibitors or memantine.[50] Despite reasons to believe that cholinesterase inhibitors might benefit patients with vascular dementia,[51] previous studies showed limited improvement on cholinesterase inhibitors.

A crucial next step in research of vascular cognitive impairment is the elucidation of the molecular pathways linking the individual vascular risk factors and cerebrovascular changes to cognitive impairment. Understanding of the specific pathways linking each of these factors to cognitive decline will help identify specific targets for treatment, and may point to appropriate treatment strategies. The exponential progress in genomics, proteomics and functional and structural brain imaging made in the past few years provides the potential to achieve this goal.

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References

1. Kalaria RN, Kenny RA, Ballard CG, Perry R, Ince P, Polvikoski T. Towards defining the neuropathological substrates of vascular dementia. Journal of the neurological sciences 2004;226(12): 75–80. [PubMed: 15537525]
2. Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. Lancet neurology 2005;4(11):752–759. [PubMed: 16239182]
3. Reitz C, Bos MJ, Hofman A, Koudstaal PJ, Breteler MM. Prestroke cognitive performance, incident stroke, and risk of dementia: the Rotterdam Study. Stroke; a journal of cerebral circulation 2008;39 (1):36–41. [PubMed: 18006863]
4. Fein G, Di Sclafani V, Tanabe J, Cardenas V, Weiner MW, Jagust WJ, Reed BR, Norman D, Schuff N, Kusdra L, Greenfield T, Chui H. Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. Neurology 2000;55(11):1626–1635. [PubMed: 11113215]
5. Jellinger KA. The pathology of ischemic-vascular dementia: an update. J Neurol Sci 2002;203-204:153–157. [PubMed: 12417375]
6. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006;368(9533):387–403. [PubMed: 16876668]
7. 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 1997;277(10):813–817. [PubMed: 9052711]
8. Wen Y, Yu WH, Maloney B, Bailey J, Ma J, Marie I, Maurin T, Wang L, Figueroa H, Herman M, Krishnamurthy P, Liu L, Planel E, Lau LF, Lahiri DK, Duff K. Transcriptional regulation of beta-secretase by p25/cdk5 leads to enhanced amyloidogenic processing. Neuron 2008;57(5):680–690. [PubMed: 18341989]
9. Wen Y, Yang SH, Liu R, Perez EJ, Brun-Zinkernagel AM, Koulen P, Simpkins JW. Cdk5 is involved in NFT-like tauopathy induced by transient cerebral ischemia in female rats. Biochimica et biophysica acta 2007;1772(4):473–483. [PubMed: 17113760]
10. Smith CD, Snowdon DA, Wang H, Markesbery WR. White matter volumes and periventricular white matter hyperintensities in aging and dementia. Neurology 2000;54(4):838–842. [PubMed: 10690973]
11. Vermeer SE, Longstreth WT Jr. Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet neurology 2007;6(7):611–619. [PubMed: 17582361]
12. Frisoni GB, Galluzzi S, Pantoni L, Filippi M. The effect of white matter lesions on cognition in the elderly--small but detectable. Nature clinical practice 2007;3(11):620–627.
13. Wright CB, Festa JR, Paik MC, Schmiedigen A, Brown TR, Yoshita M, DeCarli C, Sacco R, Stern Y. White matter hyperintensities and subclinical infarction: associations with psychomotor speed and cognitive flexibility. Stroke; a journal of cerebral circulation 2008;39(3):800–805. [PubMed: 18258844]
14. Libon DJ, Price CC, Giovannetti T, Swenson R, Bettcher BM, Heilman KM, Pennisi A. Linking MRI hyperintensities with patterns of neuropsychological impairment: evidence for a threshold effect. Stroke; a journal of cerebral circulation 2008;39(3):806–813. [PubMed: 18258842]
15. Delano-Wood L, Abeles N, Sacco JM, Wierenga CE, Horne NR, Bozoki A. Regional white matter pathology in mild cognitive impairment: differential influence of lesion type on neuropsychological functioning. Stroke; a journal of cerebral circulation 2008;39(3):794–799. [PubMed: 18258826]
16. Hachinski VC. The decline and resurgence of vascular dementia. Cmaj 1990;142(2):107–111. [PubMed: 2403832]
17. Roman GC. Senile dementia of the Binswanger type. A vascular form of dementia in the elderly. Jama 1987;258(13):1782–1788. [PubMed: 3625988]
18. Swartz RH, Stuss DT, Gao F, Black SE. Independent cognitive effects of atrophy and diffuse subcortical and thalamico-cortical cerebrovascular disease in dementia. Stroke; a journal of cerebral circulation 2008;39(3):822–830. [PubMed: 18258840]

19. Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. Archives of neurology 2007;64(4):570–575. [PubMed: 17420320]
20. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. American journal of epidemiology 2001;154 (7):635–641. [PubMed: 11581097]
21. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 1999;53(9):1937–1942. [PubMed: 10599761]
22. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. Diabetes 2002;51(4):1256–1262. [PubMed: 11916953]
23. Craft S. Insulin resistance syndrome and Alzheimer's disease: age- and obesity-related effects on memory, amyloid, and inflammation. Neurobiology of aging 2005;26(Suppl 1):65–69. [PubMed: 16266773]
24. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Oden A, Svanborg A. 15-year longitudinal study of blood pressure and dementia. Lancet 1996;347(9009):1141–1145. [PubMed: 8609748]
25. 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; a journal of cerebral circulation 1997;28(2):316–321. [PubMed: 9040682]
26. Reitz C, den Heijer T, van Duijn C, Hofman A, Breteler MM. Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. Neurology 2007;69(10):998–1005. [PubMed: 17785668]
27. Reitz C, Luchsinger J, Tang MX, Mayeux R. Effect of smoking and time on cognitive function in the elderly without dementia. Neurology 2005;65(6):870–875. [PubMed: 16186526]
28. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology. 2008
29. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64(2):277–281. [PubMed: 15668425]
30. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ (Clinical research ed 2001;322(7300):1447–1451.
31. Guo Z, Viitanen M, Fratiglioni L, Winblad B. Low blood pressure and dementia in elderly people: the Kungsholmen project. BMJ (Clinical research ed 1996;312(7034):805–808.
32. Hebert LE, Scherr PA, Bennett DA, Bienias JL, Wilson RS, Morris MC, Evans DA. Blood pressure and late-life cognitive function change: a biracial longitudinal population study. Neurology 2004;62 (11):2021–2024. [PubMed: 15184608]
33. Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. Change in body mass index and risk of incident Alzheimer disease. Neurology 2005;65(6):892–897. [PubMed: 16186530]
34. Selkoe DJ. The origins of Alzheimer disease: a is for amyloid. Jama 2000;283(12):1615–1617. [PubMed: 10735401]
35. Reaven, GM.; Laws, A. Insulin resistance: the metabolic syndrome X. Humana Press; Totowa, New Jersey: 1999.
36. Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch MP, Eckman CB, Tanzi RE, Selkoe DJ, Guenette S. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. Proceedings of the National Academy of Sciences of the United States of America 2003;100(7):4162–4167. [PubMed: 12634421]
37. Yamagishi S, Nakamura K, Inoue H, Kikuchi S, Takeuchi M. Serum or cerebrospinal fluid levels of glyceraldehyde-derived advanced glycation end products (AGEs) may be a promising biomarker for early detection of Alzheimer's disease. Medical hypotheses 2005;64(6):1205–1207. [PubMed: 15823718]
38. Nag S. Cerebral changes in chronic hypertension: combined permeability and immunohistochemical studies. Acta Neuropathol (Berl) 1984;62(3):178–184. [PubMed: 6695553]

39. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron 2008;57(2):178–201. [PubMed: 18215617]
40. Trujillo ME, Scherer PE. Adiponectin--journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. Journal of internal medicine 2005;257(2):167–175. [PubMed: 15656875]
41. Yu YH, Ginsberg HN. Adipocyte signaling and lipid homeostasis: sequelae of insulin-resistant adipose tissue. Circulation research 2005;96(10):1042–1052. [PubMed: 15920027]
42. Luchsinger JA, Tang MX, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004;63(7):1187–1192. [PubMed: 15477536]
43. Watson GS, Bernhardt T, Reger MA, Cholerton BA, Baker LD, Peskind ER, Asthana S, Plymate SR, Frolich L, Craft S. Insulin effects on CSF norepinephrine and cognition in Alzheimer's disease. Neurobiology of aging 2006;27(1):38–41. [PubMed: 16298239]
44. Nathan DM. Rosiglitazone and cardiotoxicity--weighing the evidence. The New England journal of medicine 2007;357(1):64–66. [PubMed: 17551161]
45. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, Bossini A, Fagard R, Gil-Extremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Birkenhager WH. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Archives of internal medicine 2002;162(18): 2046–2052. [PubMed: 12374512]
46. Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998;352(9137):1347–1351. [PubMed: 9802273]
47. Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Archives of internal medicine 2003;163(9):1069–1075. [PubMed: 12742805]
48. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. Journal of hypertension 2003;21(5):875–886. [PubMed: 12714861]
49. Di Bari M, Pahor M, Franse LV, Shorr RI, Wan JY, Ferrucci L, Somes GW, Applegate WB. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. American journal of epidemiology 2001;153(1):72–78. [PubMed: 11159149]
50. Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet neurology 2007;6(9): 782–792. [PubMed: 17689146]
51. Roman GC, Wilkinson DG, Doody RS, Black SE, Salloway SP, Schindler RJ. Donepezil in vascular dementia: combined analysis of two large-scale clinical trials. Dementia and geriatric cognitive disorders 2005;20(6):338–344. [PubMed: 16192723]