Relationship Between Cerebrovascular Lesions and Primary Neurodegenerative Diseases

Neuro-degenerative Diseases

Neurodegenerative Dis 2010;7:116–121
DOI: 10.1159/000285520

Published online: February 18, 2010

The Vascular Hypothesis of Alzheimer's Disease: Bench to Bedside and Beyond

Jack C. de la Torre

Banner Sun Health Research Institute, Sun City, Ariz., USA

Key Words
Echocardiography · Carotid artery ultrasound · Vascular hypothesis of Alzheimer's disease · Cerebral hypoperfusion · Cardiovascular disease · Intima media thickness · Carotid artery stenosis

Abstract
The vascular hypothesis of Alzheimer's disease (AD) which we first proposed in 1993, has become a useful concept in identifying vascular risk factors for AD or vascular dementia that can be modified through appropriate treatment to prevent, reduce or delay the onset of cognitive impairment and dementia onset. Among the more than two dozen vascular risk factors already identified for AD, are cardiovascular disease and carotid artery atherosclerosis, which may exert their pathology by chronically lowering cerebral hypoperfusion during aging. We propose and plan to initiate a clinical study to screen middle-aged, cognitively intact individuals, with carotid artery ultrasound and echocardiography to identify potentially progressive pathology in the heart and carotid artery that is considered modifiable with optimal medical treatment. This clinical strategy, if found effective in preventing pathologic conditions suspected of contributing to severe cognitive impairment, could significantly reduce AD prevalence if applied on a wide scale and help promote healthier mental and physical aging while providing a compelling economic benefit to society.

Introduction

The search for a cure for sporadic Alzheimer's disease (AD) has been elusive in the past 100 years due to a major difficulty. The loss of cognitive functions in AD patients is irrevocable because the neurons that formerly controlled these functions are likely dead and dead neurons can not be brought back to life. Inexplicably, some pharmaceutical houses have challenged this 'biological rule' by giving AD patients drugs claimed to rescue dead neurons by reducing Aβ load or clearance from the brain. This attempt to pharmacologically reverse AD symptoms or somehow affect disease outlook has ended in repeated failure during clinical trials of drugs such as AlzheMed (tramiprosate), Flurizan (tarenflurbil), AN-1792, Elan 301 and 302 (bapineuzimab). It is therefore baffling to see the same concept tested clinically over and over again while somehow expecting a different result to occur. Observers of this phenomenon may try to guess how, after more than 12,000 published papers on the role of Aβ on AD in the last 20 years, the amyloid cascade hypothesis continues to run on empty. A clue to this puzzling tactic may be found in Einstein's cynical maxim 'if the facts don't fit the theory, change the facts'.

Since neurogenesis, stem cell or other research breakthrough to replace dead neurons is still a distant prospect as a relevant solution, development of techniques that can be presently applied to reduce AD prevalence may be a more pragmatic clinical approach.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1660–2854/10/0073–0116$26.00/0

Accessible online at:
www.karger.com/ndd

J.C. de la Torre, MD, PhD
Center for Alzheimer's Research
Banner Sun Health Research Institute
Sun City, AZ 85351 (USA)
Tel. +1 760 703 0585, E-Mail jcdelatorre@comcast.net

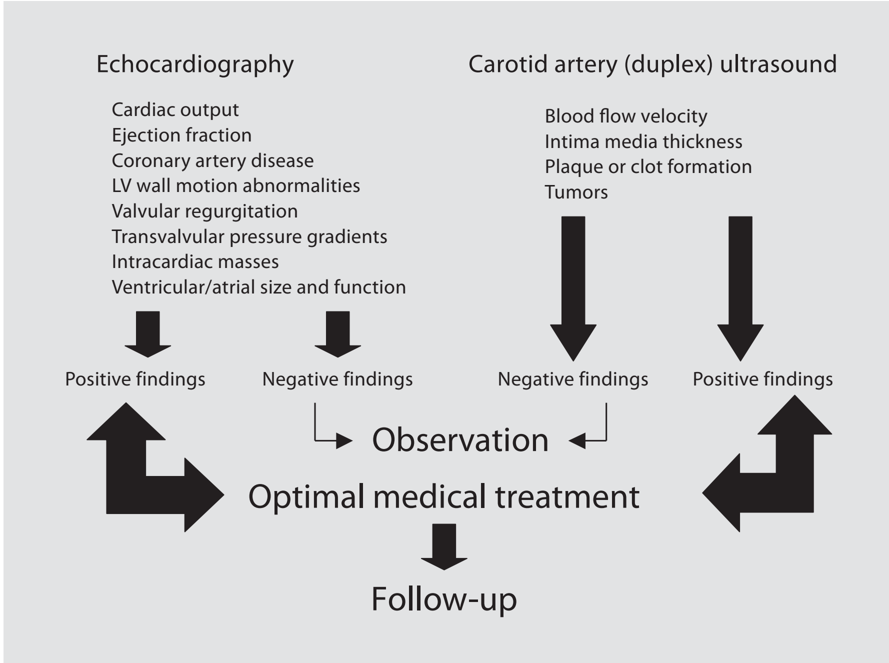

Fig. 1. Clinical flowchart for screening patients with echocardiography and carotid artery (duplex) ultrasound. Note the number of cardiovascular and carotid artery deficits that can be identified with both techniques and the possibility of using OMT and follow-up after treatment in the event positive pathologic findings are recorded. When negative pathologic findings are recorded, the patient can be monitored periodically (observation). LV = Left ventricular.

Consequently, *prevention*, rather than a *cure* of AD, appears as a more realistic stratagem to offset the catastrophic impact of this dementia whose incidence by 2050 is expected to approach nearly a million people per year in the US alone, with a total estimated prevalence of 11–16 million people affected [1].

The vascular hypothesis of AD, first proposed by us in 1993 [2], has become a mother lode of interdisciplinary research involving mainly the brain, the heart and the circulation [3–13]. The collective evidence supporting the vascular hypothesis offers the possibility of targeting vascular risk factors for AD and vascular dementia (VaD) by preventing, delaying or reversing further progression and inherent cognitive deterioration that often precede AD and VaD [14]. Following our proposal in 1993, we observed in 1994 that conditions such as advanced aging, a former head injury, apoE4 genotype, etc, were *risk factors* for AD by virtue of their lowering blood flow to the brain [15]. Since then, several dozen heterogeneous AD vascular risk factors have been reported [6, 8], including atherosclerosis and cardiovascular disease [16–22], which is the focus of this review.

A lowered prevalence of cognitive impairment by prevention or delay of atherosclerosis and cardiovascular disease in cognitively intact, middle-aged individuals may now be a rational clinical goal much like early detection and prevention of cancer using colonoscopy and mammography. We propose that this strategy may be feasible by screening with carotid artery ultrasound and echocardiography (CAUSE) [23, 24].

These screening tools are useful because they are noninvasive, cost-effective, easily applied within a 90-min session, relatively accurate procedures and pose no inherent harmful effects. More specifically, these tools can help identify patients most likely to develop progressive cognitive decline during aging as a result of mild but persistent chronic brain hypoperfusion (CBH), a reactive process that can develop decades after long-term cardiovascular and carotid artery pathology from suboptimal delivery of blood flow to the brain. Following screening with CAUSE and after careful analysis of each case, optimal medical treatment (OMT) may be recommended in patients who show subclinical evidence of carotid or cardiovascular pathology (fig. 1). OMT is defined as any medically sound therapy considered clinically indicated to prevent, delay, or reverse a condition or disease that if left alone, will likely result in worsening damage and complications. For example, antihypertensive treatment to prevent or delay premature death or organ damage is the preferred medical treatment for persistent hypertension.

In this brief review, the bench-to-bedside research that led to the vascular hypothesis of AD and what lessons can be learned from such research will be discussed in relation to how the potential prevention of cardiovascular and atherosclerotic risk factors may lessen the prevalence of cognitive decline and conversion to AD or VaD.

Bench to Bedside

The vascular hypothesis of AD is rooted in experimental studies carried out in our laboratory in the early 1990s that revealed bilateral carotid artery occlusion in an aging (but not young) rat model of CBH resulted in *persistent* and *worsening* spatial memory decline, a condition reminiscent of the progressive cognitive decline observed in AD [25]. The pathophysiologic and behavioral changes seen with the CBH model developed slowly over time and progressively worsened as a consequence of the persistent cerebral hypoperfusion [26]. Moreover, the CBH model differed from previous models of brain ischemia that generated rapid, focal and often severe, neurological impairment. The major advantages offered by the CBH model were the resulting progressive unfolding of the spatial memory decline and the expanding cascade of abnormal biochemical and subcellular events that preceded the memory loss and led eventually to cortical atrophy and death [27]. Thus, the slowly emerging pathology could be chronologically examined over many months allowing a clinical picture to develop that revealed the onset of anatomic, physiologic and memory abnormalities affecting the brain cells at the cellular and molecular level [28].

The cellular-molecular events initially targeted the ischemic-sensitive hippocampal CA1 brain cells and the posterior parietal cortex [14, 25–27], mimicking the neuropathologic process seen in early AD [29–31]. Aging rats subjected to CBH showed an immediate 34% hippocampal blood flow reduction [25] and the following sequential events: (a) impaired neuronal energy metabolism [32, 33], (b) astrocytosis [26], (c) oxidative stress [14, 33], (d) reduced protein synthesis and increased protein abnormalities [34], (e) spatial memory loss [25–27], (f) endothelial cell damage affecting vascular nitric oxide [35], (g) Aβ1–42 upregulation [35], (h) overexpression of G protein-coupled receptor kinase 2, an indicator of oxidative stress and cardiac ischemia and early marker of AD [36], and (i) brain atrophy and death [32]. Most surprisingly, the early hypometabolic changes after CBH occurred in the *absence* of *senile plaque* formation and *neurofibrillary tangles*, the hallmark pathologic deposits of AD. There was also no evidence of gray-white matter ischemic stroke damage [26].

It was clear from these findings that the CBH model did not represent VaD-like changes but rather resembled AD-like changes that ultimately involved atrophic, degenerative and progressive pathology that simulated the clinical picture characterizing AD [25–36].

We observed that the early cerebral hypometabolism and memory deficits seen soon after CBH were followed months later by the slow emergence of CA1 neurodegeneration and that the 'sole' trigger that generated the eventual corticohippocampal atrophy which developed after 10–12 months was CBH [32, 37], equivalent to about 18 human years.

Our lab-bench findings of severe cognitive and neurodegenerative pathology in aging rats subjected to CBH were confirmed by others [38, 39]. Some of the main changes associated with CBH in rats reported by others included reduced acetylcholine levels in the hippocampus [40], uncoupling of regional cerebral blood flow and cortical glucose metabolism [41, 42], impaired long-term potentiation [43] and downregulation of protein synthesis reflected by depressed mRNA microtubule associated protein-2, a marker of neurodegeneration [44]. These and our own data indicated that experimental CBH in aging rats led to symptoms and signs reminiscent of the pathologic process seen prior to and during the development of AD.

If no neuropathological 'hallmarks' of AD or VaD were present after CBH in the aging rats, what did their progressive cognitive and degenerative pathology reflect? Could it be that plaque or tangle deposits do not play a central role in the pathophysiology of AD (like rats) and CBH generated from vascular risk factors is the main trigger (like rats) of the neurodegenerative cascade during advanced aging? In support of the first part of this notion, a number of studies have indicated that substantial Aβ burden can be found in cognitively intact older people even though the plaque and tangle distribution, density and topographical progression of these 'hallmark' deposits is the same as that seen in symptomatic AD patients [45–48]. Significant Aβ brain deposition does not appear to be associated with worse cognitive function [49]. In addition, virtual clearing of plaques from human brain with Aβ42 immunization does not prevent progressive neurodegeneration or the advancing severity of AD [50].

Beyond the Bedside

The concept that AD may be a vascular disorder with neurodegenerative consequences [2, 51] has offered a verifiable explanation into the nature of this disorder and opened the authentic possibility of preventing AD by targeting its reported vascular risk factors, such as cardiovascular disease and atherosclerosis [16, 22]. We have previously discussed the application and benefits of CAUSE in the prevention-by-detection of severe cognitive impairment from cardiac-carotid pathology [23, 24], and for brevity's sake will only refer to this technology in a clinical flowchart (fig. 1).

The ability to accurately measure cardiac function and carotid artery pathology using CAUSE in asymptomatic or symptomatic individuals is important in clinical practice because it may detect functional and structural abnormalities at an early stage that may progress irreversibly in severity if left untreated. CAUSE, like colonoscopies that are used to prevent cancer, would be less costly than a colonoscopy and would offer the possibility of treating a preventable disorder at a stage when intervention may be most effective. There is presently no clinical screening test that can identify potential candidates at risk of cognitive dysfunction and dementia in a population who have no apparent symptoms of the diseases being screened. CAUSE may offer this possibility. Once individuals with carotid artery-cardiac pathology are identified, additional diagnostic tests can be performed to try and confirm the ultrasound findings with greater certainty.

Figure 1 shows a clinical plan to screen cognitively intact middle-aged individuals for subclinical cardiovascular disease and carotid artery atherosclerosis that can slow or prevent CBH, a presumed promoter of cognitive decline. The plan calls for early OMT when indicated, to try and prevent further progression of specific cardiovascular and carotid artery deficits identified using CAUSE (fig. 1). If OMT is not indicated, the practitioner may recommend lifestyle changes to the patient which can foster a healthier mental and physical outlook [52].

It is reasonable to assume that OMT which can prevent or delay the rate of disease progression, would also improve the identified pathological deficit, whether it is regression or stabilization of carotid artery plaque formation, intima media thickness or a cardiovascular abnormality detected by echocardiography.

Although a number of studies have linked cardiovascular disease and atherosclerosis with cognitive decline [3, 4, 6, 7, 10, 11, 46], and with AD or VaD [6, 8, 12, 16, 18, 20, 50, 53, 54], it remains speculative at present to assume that screening and treating these conditions before they become symptomatic will have a significant impact on the number of new dementia cases recorded annually. The clinical plan to screen individuals with CAUSE and when indicated, start early OMT or patient monitoring to prevent or delay further progression of specific cardiovascular-carotid artery pathology, could, if validated, significantly help reduce the prevalence of AD and VaD in the years to come. For these reasons, a feasibility study such as we have proposed [23, 24], needs to be done to test the merit and practicality of CAUSE screening in cognitively intact individuals. On the other hand, if nothing is done, or if clinical trials can only repeat past clinical failures, progress in dementia research will continue at a glacial pace. It is important to remember that a 5-year delay in the onset of AD could reduce the prevalence of AD by 50% [55] and the relative annual costs presently estimated at 100 billion dollars in the US alone [1]. We are therefore planning to test the merit of CAUSE in a preliminary clinical study of cognitively healthy, middle-aged population and offer this discussion for investigators to consider this clinical strategy.

Acknowledgment

This research was supported by an Investigator-Initiated Research Grant from the Alzheimer's Association.

References

1 Alzheimer's Association: 2009 Alzheimer's disease facts and figures. Alzheimers Dement 2009;5:234–270.
2 de la Torre JC, Mussivand T: Can disturbed brain microcirculation cause Alzheimer's disease? Neurol Res 1993;15:146–153.
3 Caselli RJ, Chen K, Lee W, Alexander GE, Reiman EM: Correlating cerebral hypometabolism with future memory decline in subsequent converters to amnestic pre-mild cognitive impairment. Arch Neurol 2008;65: 1231–1236.
4 Roher AE, Esh C, Kokjohn TA, Kalbak W, Luhers DC, Seward JD, Sue LI, Beach TG: Circle of Willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. Arterioscler Thromb Vasc Biol 2003;23:2055–2062.
5 Milionis HJ, Florentin M, Giannopoulos S: Metabolic syndrome and Alzheimer's disease: a link to a vascular hypothesis? CNS Spectr 2008;13:606–613.

6 Helzner E, Luchsinger J, Scarmeas N, Cosentino S, Brickman A, Glymour M, Stern Y: Contribution of vascular risk factors to the progression in Alzheimer disease. Arch Neurol 2009;66:343–348.
7 Aguero-Torres H, Kivipelto M, von Strauss E: Rethinking the dementia diagnoses in a population-based study: what is Alzheimer's disease and what is vascular dementia? A study from the Kungsholmen project. Dement Geriatr Cogn Disord 2006;22:244–249.
8 Breteler MM: Vascular risk factors for Alzheimer's disease: an epidemiological study. Neurobiol Aging 2000;21:153–160.
9 Dede DS, Yavuz B, Yavuz BB, Cankurtaran M, Halil M, Ulger Z, Cankurtaran ES, Aytemir K, Kabakci G, Ariogul S: Assessment of endothelial function in Alzheimer's disease: is Alzheimer's disease a vascular disease? J Am Geriatr Soc 2007;55:1613–1617.
10 Beach TG, Wilson JR, Sue LI, Newell A, Poston M, Cisneros R, Pandya Y, Esh C, Connor DJ, Sabbagh M, Walker DG, Roher AE: Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta Neuropathol 2007;113:13–21.
11 Ruitenberg A, den Heiker T, Bakker SL: Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam study. Ann Neurol 2005;57:789–794.
12 Lindsay J, Laurin D, Verreault R, et al: Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 2002;156:445–453.
13 de la Torre JC: How do heart disease and stroke become risk factors for Alzheimer's disease? Neurol Res 2006;28:637–644.
14 de la Torre JC, Cada A, Nelson N, Davis G, Sutherland RJ, Gonzalez-Lima F: Reduced cytochrome oxidase and memory dysfunction after chronic brain ischemia in aged rats. Neurosci Lett 1997;223:165–168.
15 de la Torre JC: Impaired brain microcirculation may trigger Alzheimer's disease. Neurosci Behav Rev 1994;18:397–401.
16 Hofman A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F: Atherosclerosis, apolipoprotein E and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 1997;349:151–154.
17 Casserly I, Topol E: Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 2004;363:1139–1146.
18 van Oijen M, de Jong FJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM: Atherosclerosis and risk for dementia. Ann Neurol 2007;61:403–410.
19 de la Torre JC: Is Alzheimer's a neurodegenerative or a vascular disorder? Data, dogma and dialectics. Lancet Neurol 2004;3:184–190.
20 Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K: Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64:277–281.
21 Kilander L, Andren B, Nyman H, Lind L, Boberg M, Lithell H: Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men. Stroke 1998;29:1816–1820.
22 Zuccalà G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R: Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. J Neurol Neurosurg Psychiatry 1997;3:509–512.
23 de la Torre JC: Alzheimer's disease prevalence can be lowered with non-invasive testing. J Alzheimers Dis 2008;14:353–359.
24 de la Torre JC: Carotid artery ultrasound and echocardiography (CAUSE) testing to lower the prevalence of Alzheimer's disease. J Stroke Cerebrovasc Dis 2009;18:319–328.
25 de la Torre JC, Fortin T, Park G, Butler K, Kozlowski P, Pappas B, de Socarraz H, Saunders J, Richard M: Chronic cerebrovascular insufficiency induces dementia-like deficits in aged rats. Brain Res 1992;582:186–195.
26 de la Torre JC, Fortin T, Park Saunders J, Kozlowski P, Butler K, de Socarraz H, Pappas B, Richard M: Aged but not young rats develop metabolic, memory deficits after chronic brain ischemia. Neurol Res 1992; 14(suppl):177–180.
27 de la Torre JC, Fortin T, Park G, Pappas B, Saunders J, Richard M: Brain blood-flow restoration 'rescues' chronically damaged rat CA1 neurons. Brain Res 1993;623:6–15.
28 de la Torre JC, Pappas BA, Fortin T, Keyes M, Davidson C: Progressive neurodegeneration in rat brain after chronic 3-VO or 2-VO; in Fiskum G (ed): Neurodegenerative Diseases. New York, Plenum Press, pp 77–84, 1996.
29 Matsuda H: The role of neuroimaging in mild cognitive impairment. Neuropathology 2007;27:570–577.
30 Rodriguez G, Vitali P, Calvini P, Bordoni C, Girtler N, Taddei G, Mariani G, Nobili F: Hippocampal perfusion in mild cognitive impairment. Psychiatry Res 2000;100:65–74.
31 Mosconi L, Mistur R, Switalski R, Tsui WH, Glodzik L, Li Y, Pirraglia E, De Santi S, Reisberg B, Wisniewski T, de Leon MJ: FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. Eur J Nucl Med Mol Imaging 2009;36:811–822.
32 de la Torre JC, Fortin T, Saunders J: Correlates between NMR spectroscopy, diffusion weighted imaging and CA1 morphometry following chronic brain ischemia. J Neurosci Res 1995;41:238–245.
33 Cada A, de la Torre JC, Gonzalez-Lima F: Chronic cerebrovascular ischemia in aged rats: effects of brain metabolic capacity and behavior. Neurobiol Aging 2000;21:225–234.
34 Abdollahian NP, Cada A, Gonzalez-Lima F, de la Torre JC: Cytochrome oxidase: a predictive marker of neurodegeneration; in Gonzalez-Lima F (ed): Cytochrome Oxidase in Neuronal Metabolism and Alzheimer's Disease. New York, Plenum Press, 1998, pp 233–261.
35 de la Torre JC, Aliev G: Inhibition of vascular nitric oxide after rat chronic brain hypoperfusion: spatial memory and immunocytochemical changes. J Cerebral Blood Flow Metab 2005;25:663–672.
36 Obrenovich ME, Smith MA, Siedlak SL, Chen SG, de la Torre JC, Perry G: Overexpression of GRK2 in Alzheimer disease and in a chronic hypoperfusion rat model is an early marker of brain mitochondrial lesions. Neurotox Res 2000;10:43–56.
37 De Jong GI, Farkas E, Stienstra CM, Plass JR, Keijser JN, de la Torre JC, Luiten PG: Cerebral hypoperfusion yields capillary damage in the hippocampal CA1 area that correlates with spatial memory impairment. Neuroscience 1999;91:203–210.
38 Sopala M, Danysz W: Chronic cerebral hypoperfusion in the rat enhances age-related deficits in spatial memory. J Neural Transm 2001;108:1445–1456.
39 Farkas E, Luiten PG: Cerebral microvascular pathology in aging and Alzheimer's disease. Prog Neurobiol 2001;64:575–611.
40 Ni JW, Matsumoto K, Li HB, Murakami Y, Watanabe H: Neuronal damage and decrease of central acetylcholine level following permanent occlusion of bilateral common carotid arteries in rat. Brain Res 1995;673:290–296.
41 Otori T, Katsumata T, Muramatsu H, Kashiwagi F, Katayama Y, Terashi A: Long-term measurements of cerebral blood flow and metabolism in a rat chronic hypoperfusion model. Clin Exp Pharmacol Physiol 2003;30: 266–272.
42 Tsuchiya M, Sako K, Yura S, Yonemasu Y: Local cerebral glucose utilisation following acute and chronic bilateral carotid artery ligation in Wistar rats: relation to changes in local cerebral blood flow. Exp Brain Res 1993;95:1–7.
43 Sekhon LH, Spence I, Morgan MK, Weber NC: Chronic cerebral hypoperfusion inhibits its calcium-induced long-term potentiation in rats. Stroke 1997;28:1043–1048.
44 Liu HX, Zhang JJ, Zheng P, Zhang Y: Altered expression of MAP-2, GAP-43, and synaptophysin in the hippocampus of rats with chronic cerebral hypoperfusion correlates with cognitive impairment. Brain Res Mol Brain Res 2005;139:169–177.
45 Schmitt FA, Davis DG, Wekstein DR, Smith CD, Ashford JW, Markesbery WR: 'Preclinical' AD revisited: neuropathology of cognitively normal older adults. Neurology 2000; 55:370–376.

46 Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ, Smith GE, Dickson DW, Johnson KA, Petersen LE, McDonald WC, Braak H, Petersen RC: Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol 2003;62:1087–1095.
47 Giannakopoulos P, Herrmann FR, Bussire T, et al: Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. Neurology 2003;60:1495–1500.
48 Davis DG, Schmitt FA, Wekstein DR, Markesbery WR: Alzheimer neuropathologic alterations in aged cognitively normal subjects. J Neuropathol Exp Neurol 1999;58:376–388.
49 Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, Ziolko SK, James JA, Snitz BE, Houck PR, Bi W, Cohen AD, Lopresti BJ, DeKosky ST, Halligan EM, Klunk WE: Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol 2008;65:1509–1517.
50 Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JA: Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. Lancet 2008;372:216–223.
51 de la Torre JC: Critically attained threshold of cerebral hypoperfusion (CATCH): can it cause Alzheimer's disease? Ann NY Acad Sci 2000;903:424–436.
52 Solfrizzi V, Capurso C, D'Introno A, Colacicco AM, Santamato A, Ranieri M, Fiore P, Capurso A, Panza F: Lifestyle-related factors in predementia and dementia syndromes. Expert Rev Neurother 2008;8:133–158.
53 Singh-Manoux A, Sabia S, Lajnef M, Ferrie JE, Nabi H, Britton AR, Marmot MG, Shipley MJ: History of coronary heart disease and cognitive performance in midlife: the Whitehall II study. Eur Heart J 2008, Epub ahead of print.
54 Zhiyou C, Yong Y, Shanquan S, Jun Z, Liangguo H, Ling Y, Jieying L: Upregulation of BACE1 and beta-amyloid protein mediated by chronic cerebral hypoperfusion contributes to cognitive impairment and pathogenesis of Alzheimer's disease. Neurochem Res 2009;34:1226–1235.
55 Brookmeyer R, Gray S, Kawas C: Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health 1998;88:1337–1342.