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Review

Vascular risk factor detection and control may prevent Alzheimer's disease

Jack C. de la Torre*

Center for Alzheimer's Research, Banner Sun Health Research Institute, Sun City, AZ 85351, United States

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ABSTRACT

The vascular hypothesis of Alzheimer disease (AD), first proposed by us in 1993, provides substantial evidence that suggests vascular risk factors (VRF) play a critical role in the development of cognitive decline and AD during aging. Cardiovascular and carotid artery disease, two major risk factors to AD, can conspire or independently induce chronic brain hypoperfusion (CBH) decades before any symptoms of cognitive impairment are expressed. The pathologic construct linking CBH to cognitive impairment and AD remains unclear but evidence shows that it may provide an opportunity to intervene in the prevention or delay of dementia onset. A preliminary randomized clinical study in cognitively healthy middle age individuals to undergo screening using carotid Doppler ultrasound, echocardiography and ankle-brachial index is proposed. These office tools are non-invasive, cost-effective, easily applied in one session and relatively accurate procedures with no inherent harmful effects. More importantly, ultrasound can help identify asymptomatic patients most likely to develop progressive cognitive decline due to persistent CBH secondary to progressive cardiovascular or carotid artery pathology. When these VRF are detected within the heart or carotid arteries, optimal medical treatment or management may be indicated to prevent or slow down further disease progression that fosters cognitive deterioration generated from such conditions. Secondary screening tools such as neuroimaging, neurocognitive testing and CSF markers may be used to confirm ultrasound findings. Prevention-by-detection of VRF and target treatment, if found effective, could significantly promote healthier mental and physical aging and lessen the socio-economic calamity anticipated from the growing prevalence of dementia.

1. Background

Alzheimer's disease (AD) has become one of the most cataclysmic medical problems of the 21st century with annual costs estimated at over 100 billion dollars (Zhu et al., 2006) in the U.S. alone and an expected prevalence growing exponentially to over 13 million Americans affected by 2050 (Hebert et al., 2003).

Finding a cure for sporadic AD using the available present technology is unlikely for one compelling reason. Dead brain neurons cannot be brought back to life. While stem cell research, neurogenesis or some other research breakthrough may one day replace dead neural networks (though not their consolidated memory imprint), that technology is distant. Moreover, replacing brain cells which prior to their neurodegeneration were charged with modulating emotions, memory, abstraction, reasoning, language and other cognitive skills that define the individual, can not be done without creating a new personal identity. For that reason, the catastrophic cognitive loss observed in AD patients cannot improve even if the neurodegenerative progress is somehow delayed or arrested.

Because a cure for AD seems unlikely, (de la Torre, 2009) *prevention* aimed at the asymptomatic, individual found to show vascular risk factors to cognitive impairment appears as the most operable alternative. Cognitive impairment is now considered by many investigators to be a transitional stage prodromal to dementia. Delaying the onset of AD for 2 or 5 years by preventive measures, can result in a significant lowering of 20–50% new cases every year (Brookmeyer et al., 1998).

Primary medical disorders generally lessening cerebral perfusion and unhealthy lifestyle are reported risk factors to AD (Tables 1 and 2) and many of these conditions are vascular-related and modifiable.

Eliminating or lowering the impact of risk factors identified to foster cognitive decline during aging could be achieved if clinically detected, staged as mild, moderate or high risk, and properly managed or treated (de la Torre, in press). For example, major vascular risk factors to AD known to reduce cerebral perfusion, such as atherosclerosis and cardiovascular pathology, which are the focus of this review, can be present in asymptomatic subjects decades before cognitive impairment is expressed (Vermeer et al., 2003; Zuccalà et al., 1997). Armed with this knowledge, prevention of AD as a clinical strategy should seek to reduce or prevent the development of disorders that pose a risk to cognitive decline at a later time. This is best accomplished by early detection and treatment (when

* Tel.: +1 760 703 0585; fax: +1 623 876 5378.
E-mail address: jcdelatorre@comcast.net.

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Table 1
List of vascular risk factors (VRF) that have been described in longitudinal epidemiological studies. Possible outcome examines mainly the anticipated sequelae from VRF reported to promote cognitive impairment. References listed are not comprehensive but selectively representative. Many of the VRF listed here are commonly associated with CBH, a correlate that may be coincidental or one with important pathological significance.

AD primary vascular risk factors		
Vascular risk factor	Possible outcome	Reference
Hypertension	Stroke, CVD, hypoxia CVR, CBH, ECD, OS	(de la Torre, in press; Duron and Hanon, 2008; Reitz et al., 2007; Breteler, 2000; Villeneuve et al., 2009; Cechetto et al., 2008; Newman et al., 1993; Scuteri et al., 2005)
Hyperlipidemia	ABa, stroke, CVD, ECD	(Luchsinger and Mayeux, 2004; de la Torre, 2002a; Ruitenberg et al., 2005; Cechetto et al., 2008)
Diabetes type 2	CMA, CVD, CBH, IR, IDE	(de la Torre, in press; Duron and Hanon, 2008; Luchsinger and Mayeux, 2004; Ruitenberg et al., 2005; Breteler, 2000; Cechetto et al., 2008)
Metabolic syndrome (obesity, hypertension)	Stroke, CVD, IR	(Duron and Hanon, 2008; de la Torre, 2006; Bhargava et al., 2006)
Cardiovascular disease	Stroke, CBH, HF	(Zuccalà et al., 1997; de la Torre, 2006; Vogels, 2007; Singh-Manoux et al., 2008; Whitmer et al., 2005; Muller, 2007; de la Torre, 2002b; Aronow, 2008)
Carotid artery atherosclerosis	Stroke, CBH, ECD, OS	(de la Torre, in press; de la Torre, 2006; Haley et al., 2007; Silvestrini et al., 2009; Aichner et al., 2009; Johnston et al., 2004; Hofman et al., 1997; Wendell et al., 2009)

Vascular risk factors to Alzheimer's disease (AD) includes hypertension, hyperlipidemia, diabetes mellitus type 2 and metabolic syndrome continue to be investigated in clinical studies and together with atherosclerosis and cardiac disease, may constitute major targets for medical intervention since they are estimated to affect millions of people worldwide. Application of appropriate management or optimal medical treatment, when indicated, needs to be considered when these risk factors are detected to prevent or delay further disease progression and potential physical and cognitive damage that can convert to dementia.
Key: Aba = Abeta accumulation; CBH = chronic brain hypoperfusion; CVR = cerebrovascular resistance; ECD = endothelial cell dysfunction; CMA = cerebromicrovascular abnormalities; IDE = insulin degrading enzyme; IR = insulin resistance; MI = myocardial infarction; OS = oxidative stress.

indicated) of reported primary risk factors associated with cognitive impairment and final stage dementia. Prevention should start at middle age (and ideally earlier) in cognitively intact individuals in order to achieve a greater effect from treatments.

Assessment of AD risk should include a detailed clinical examination emphasizing the heart–brain loop, including the peripheral vascular system. In the event single or multiple risk factors to AD are detected, (Table 1) prompt, decisive action using optimal medical treatment (OMT) must be considered when indicated. OMT refers to any evidence-based, medically sound procedure considered clinically useful to delay, arrest or reverse a risk factor, a health and condition or a disease that if left alone, will presumably result in worsening complications.

The purpose of this brief review is to examine the use of carotid artery ultrasound (CAUS), echocardiography (E) and ankle–brachial index (ABI) all which are non-invasive, cost-effective and relatively reliable clinic office tools, as potential detectors of cardiovascular (CDV) and cerebrovascular (CBV) primary risk factors reported to promote cognitive impairment. If CDV and or CBV risk factors are detected using CAUSE + ABI, application of appropriate OMT, may be considered to help prevent or delay cognitive deterioration that can lead to AD or to vascular dementia (VaD). Co-exixting or independent lifestyle risk factors to dementia (Table 2) similarly, are red flags that should alert the practitioner to recommend a course of action that can extend quality life and mental health.

2. Rationale for early prevention-by-detection of risk factors

A fundamental observation in human physiology is that as we normally age, blood flow to tissues, including brain, modestly diminishes (Lakatta, 1993). By age 65, blood flow to the brain may have declined 20% of what it was at age 20 (Leenders et al., 1990). Additionally, cardiac output (CO) declines slightly while arterial stiffening increases during aging fed by atherosclerosis, hypertension, and other precursors of heart disease (Duron and Hanon, 2008; Elias et al., 2009). Parallel to the decline of cerebral perfusion during aging are the subjective memory complaints experienced by healthy individuals (Luo and Craik, 2008). These subjective complaints often lead to more progressive cognitive decline (Schofield et al., 1997). Since cognitive decline during aging is commonly prodromal to AD or to vascular dementia (VaD), treating disease harbingers, such as cerebrovascular and cardiovascular risk factors, may be one of the most important prevention strategies aimed at either dementia (de la Torre, 2006). A typical example is seen in subtle declines of executive functioning and visual memory, as determined by processing speed tests that arise in asymptomatic persons with subcortical white matter disease of vascular origin (Kramer et al., 2002).

Even suboptimal functional brain changes associated with chronic hypoperfusion can affect the brain's ability to process information quickly and efficiently despite an absence of white matter lesions or in the presence of normal global cognition, language and memory (Haley et al., 2007). A critical review of heart disease studies realized so far concludes that the two most likely pathophysiological triggers responsible for cognitive dysfunction, are cerebral hypoperfusion and multiple cardiogenic emboli (Vogels, 2007). Although cerebral microemboli can induce VaD, cerebral hypoperfusion may account for the majority of cardiac and carotid artery risk factors involved in cognitive impairment (Vogels, 2007) that can lead to AD (de la Torre, 2006). For example, cardiogenic factors promoting impaired cognition

Table 2
Several epidemiological studies report a relationship between the healthy undertaking of physical, diet, social and mental-related activities with positive effects on cognitive function and their undertaking poses the opportunity to slow down cognitive decline during advanced aging. Aerobic exercise is reported to increase cerebral perfusion in the elderly, an activity that may lower cerebrovascular disease risk in this population (see Ref. Yao et al., 1969). Modification of lifestyle risks to cognitive impairment could presumably aid in the medical intervention (Table 1) of vascular risk factors to cardiovascular and carotid artery atherosclerosis but this evidence awaits further research.

AD lifestyle preventive changes		
Risk factor	Possible outcome	Reference
Physical inactivity	Stroke, CVD, CBH	(Ainslie et al., 2008; Boyle et al., 2009)
Hyperlipidemia/hypercholesterolemia	Stroke, CVD	(Morley and Banks, in press; Martins et al., 2009)
Mental inactivity	CBH, OS	(Andrade and Radhakrishnan, 2009; Solfrizzi et al., 2008)
Smoking	Stroke, CBH, CVD, hypoxia,	(Breteler, 2000; Cataldo et al., 2010)
Obesity	Stroke, CVD, IR	(Kivipelto et al., 2005)