

Vascular factors in neurodegenerative diseases: a path towards treatment and prevention

A solid body of clinical, imaging, epidemiological and neuropathological evidence has accumulated over the past two decades confirming the critical role of cerebrovascular disease in Alzheimer disease (AD) and other dementias of the aged (Chui et al., 2006; Schneider et al., 2007; Wharton et al., 2011; Gorelick et al., 2011; Yarchoan et al., 2012; DeCarli, 2013; Bennet et al., 2013; Yates et al., 2014). Data from the National Alzheimer's Coordinating Center (Toledo et al., 2013) have shown the presence of vascular pathology in 80% of 4,629 brains from patients with neuropathologically confirmed AD. Lesions included large-vessel disease with atherosclerosis in the arteries of the circle of Willis and its branches resulting in large territorial infarcts, small-vessel disease with arteriolosclerosis and small infarcts including lacunes and multiple microinfarcts, ischemic periventricular leukoencephalopathy and brain hemorrhages. Notably, cerebral amyloid angiopathy was present in fewer than half of the brains (41%).

A striking feature of these vascular changes is their common occurrence with advancing age, even among cognitively normal, community-dwelling individuals (Longstreth et al., 2002; DeCarli, 2013; Raji et al., 2012; Rosano et al., 2013). White matter lesions are associated with increased long-term mortality but the risk is attenuated for those with higher cognitive function (Rosano et al., 2013). There is a frequent association between white matter hyperintensities and increased future risk of cerebral infarction, as well as accelerated brain atrophy of ischemic origin particularly in the frontal cortex (Raji et al., 2012). In this latter study, regression analyses revealed links among white matter changes, age, the APOE e4 allele and hypertension.

Thus, it appears evident that most cases of AD in the aged population are mixed dementias, resulting from a combination of cerebrovascular disease and neurodegeneration (Schneider et al. 2007; Savva et al., 2009; Bennett et al., 2013). These cases were traditionally known as "senile" dementias and are now diagnosed as AD. Forms of AD without a vascular component are relatively rare and occur almost exclusively in genetically determined familial cases of AD due to gene mutations, such as the E280A presenilin-1 (*PSEN1*) gene mutation (Lopera et al., 1997). In these early-onset dementias, the clinical manifestations are different from those of the senile form of AD. Onset may be as early as 34 years (mean age 46.8 years), presenting with headaches, memory and language loss, behavior and personality changes and, in the final stages, frequent gait disturbances, seizures and myoclonus; death ensues after a mean duration of about eight years.

Neuropathological reanalysis of Alzheimer's first case, Auguste Deter, has shown that she had a mutation of the *PSEN1* gene (Müller et al., 2013). Therefore it can be said that Kraepelin (1910) was correct in classifying her as a "pre-senile" form of dementia in the 8th edition of his influential *Lehrbuch der Psychiatrie*. Thus, Kraepelin introduced the novel concept of pre-senile dementia (AD), distinguishing this form from the former single group of the senile dementias (the chapter was titled *Das senile und präsenile Irresein*); second, he concluded that the most frequent form of senile dementia was arteriosclerotic insanity (*Das arteriosklerotische Irresein*, arteriosclerotic psychosis), also known as cerebral arteriosclerosis. Of interest, DSM-5 has eliminated the term dementia and returned to less specific criteria for a condition called major or mild neurocognitive disorder due to Alzheimer's disease. Also, vascular dementia has disappeared to be replaced by major or mild vascular cognitive disorder (Román, 2014; Sachdev et al., 2014).

Cerebrovascular disease is known to be associated with factors such as hypertension, hypercholesterolemia, sedentary lifestyle, obesity, diabetes mellitus type II, smoking and obstructive sleep apnea (Gorelick et al., 2011; Davis et al., 2013; de Bruijn et al., 2014). These factors have in common the fact that they are preventable and/or treatable. The actual mechanisms linking vascular injury and neurodegeneration remain to be defined (Zlokovic, 2011; Toledo et al., 2012), but they may offer novel therapeutic approaches. For instance, treatment of hyperhomocysteinemia with B-group vitamins has been shown to halt cortical atrophy in patients with mild cognitive impairment (Douaud et al., 2013). In conclusion, in view of the absence so far of an effective treatment to prevent or decelerate the progression of AD, the current emphasis needs to be on dementia prevention by appropriate treatment of the above disorders known collectively as vascular risk factors (Barnes and Yaffe, 2011; Román et al., 2012; Willis and Hakim, 2013).

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References

- Barnes DE, Yaffe K (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 10:819-828.
- Bennett DA, Wilson RS, Arvanitakis Z, et al (2013). Selected findings from the Religious Orders Study and Rush Memory and Aging Project. *J Alzheimer Dis* 33 (Suppl 1):S397-S403.
- Chui HC, Zarow C, Mack WJ, et al (2006). Cognitive impact of subcortical vascular and Alzheimer's disease pathology. *Ann Neurol* 60:677-687.
- Davis AP, Billings ME, Longstreth WT Jr, et al (2013). Early diagnosis and treatment of obstructive sleep apnea after stroke: Are we neglecting a modifiable stroke risk factor? *Neurol Clin Pract* 3:192-201.
- de Bruijn RF, Akoudad S, Cremers LG, Hofman A, et al. (2014) Determinants, MRI correlates, and prognosis of mild cognitive impairment: the Rotterdam Study. *J Alzheimers Dis* May 13, 2014 [Epub ahead of print] PMID: 24825566
- DeCarli C (2013). Clinically asymptomatic vascular brain injury: A potent cause of cognitive impairment among older individuals. *J Alzheimers Dis* 33 (Suppl 1): S417-S426
- Douaud G, Refsum H, de Jager CA, et al (2013). Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. *Proc Natl Acad Sci U S A* 110:9523-9528.
- Kraepelin E (1910). Das senile und präsenile Irresein. In: *Psychiatrie: Ein Lehrbuch für Studierende und Ärzte*. Leipzig, Johann Ambrosius Barth, pp. 533-632.
- Gorelick PB, Scuteri A, Black SE, et al (2011). Vascular contributions to cognitive impairment and dementia: a statement for health-care professionals from the American Heart Association/American Stroke Association. *Stroke* 42:2672-2713.
- Longstreth WT Jr, Dulberg C, Manolio TA, Lewis MR, et al (2002). Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke* 33:2376-2382.
- Lopera F, Ardilla A, Martínez A, et al (1997). Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation. *JAMA* 277:793-799.
- Müller U, Winter P, Graeber MB (2013). A presenilin 1 mutation in the first case of Alzheimer's disease. *Lancet Neurol* 12:129-130.
- Raji CA, Lopez OL, Kuller LH, et al. (2012) White matter lesions and brain gray matter volume in cognitively normal elders. *Neurobiol Aging* 33:834.e7-16.
- Román GC (2014) Vascular neurocognitive disorder. Chapter 66. In Gabbard GO (Ed) *Gabbard's Treatments of Psychiatric Disorders*. Fifth Edition. Chigaco IL, American Psychiatric Association.
- Román GC, Nash DT, Fillit H (2012). Translating current knowledge into dementia prevention. *Alzheimer Dis Assoc Disord* 26:295-299.
- Rosano C, Chang YF, Kuller LH, et al (2013). Long-term survival in adults 65 years and older with white matter hyperintensity: association with performance on the digit symbol substitution test. *Psychosom Med* 75:624-631.
- Sachdev P, Kalaria R, O'Brien J, et al (2014). Diagnostic criteria for Vascular Cognitive Disorders: A VASCOG Statement. *Alzheimer Dis Assoc Disord* [Epub ahead of print] PMID: 24632990
- Savva GM, Wharton SB, Ince PG, et al. (2009) Age, neuropathology, and dementia. *N Engl J Med* 360:2302-2309.
- Schneider JA, Arvanitakis Z, Bang W, et al (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 69:2197-2204.
- Toledo JB, Toledo E, Weiner MW, et al (2012). Cardiovascular risk factors, cortisol, and amyloid-beta deposition in the Alzheimer's Disease Neuroimaging Initiative. *Alzheimers Dement* 8:483-489.
- Toledo JB, Arnold SE, Raible K, et al (2013). Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain* 136:2697-2706.
- Wharton SB, Brayne C, Savva GM, et al. (2011). Epidemiological neuropathology: the MRC Cognitive Function and Aging Study experience. *J Alzheimers Dis* 25:359-372.
- Willis KJ, Hakim AM (2013). Stroke prevention and cognitive reserve: emerging approaches to modifying risk and delaying onset of dementia. *Front Neurol* 4:13.
- Yarchoan M, Xie SX, Kling MA, et al (2012). Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. *Brain* 135:3749-3756.
- Yates PA, Desmond PM, Phal PM, et al (2014). Incidence of cerebral microbleeds in preclinical Alzheimer disease. *Neurology* 82:1266-1273.
- Zlokovic BV (2011) Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci* 12:723-738.