Alzheimer's & Dementia 11 (2015) 710-717

Alzheimer's & Dementia

Review Article

# Vascular contributions to cognitive impairment and dementia including Alzheimer's disease

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**Abstract** Scientific evidence continues to demonstrate the linkage of vascular contributions to cognitive impairment and dementia such as Alzheimer's disease. In December, 2013, the Alzheimer's Association, with scientific input from the National Institute of Neurological Disorders and Stroke and the National Heart, Lung and Blood Institute from the National Institutes of Health, convened scientific experts to discuss the research gaps in our understanding of how vascular factors contribute to Alzheimer's disease and related dementia. This manuscript summarizes the meeting and the resultant discussion, including an outline of next steps needed to move this area of research forward.


*Keywords:* Alzheimer's disease; Dementia; Biomarkers; Animal models; Vascular dementia; Small vessel disease

## 1. Introduction

A recent scientific statement from the American Heart Association (AHA) and American Stroke Association highlighted the significance of vascular contributions to cognitive impairment and dementia [1], coined "VCID" here and alternatively referred to as vascular dementia and/or vascular cognitive impairment and/or vascular contributions to dementia. This link between ischemic vascular disease and dementia is clinically relevant as the former is largely preventable by optimizing the identification and management of vascular risk factors. The concept for

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http://dx.doi.org/10.1016/j.jalz.2014.10.008
1552-5260/

VCID emerged as a leading priority at the National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) hosted Stroke Research Priorities Meeting [2] and also at the 2013 Alzheimer's Disease-Related Dementia (ADRD) Summit. The ADRD Summit set two major research priorities for white matter and grey matter small vessel VCID research over the next 5–10 years including: developing experimental models to identify mechanisms and novel targets and encouraging basic science investigation of the impact of AD risk factors on cerebrovascular function and vice versa; and the development of biomarkers for clinical research and trials [3,4]. The Alzheimer's Association, with scientific input from the NINDS and the National Heart, Lung and Blood Institute (NHLBI) at NIH, convened a panel of cross-disciplinary experts in Chicago, IL, on December 17, 2013 to determine the state of the science and identify key gaps, including unanswered research questions, which when addressed, are predicted to translate into improved clinical outcomes related to small vessel VCID. This manuscript summarizes the proceedings of this discussion.

## 2. State of the science

Decades of data, including landmark work from the Honolulu Asia Aging Study [5], the Rotterdam Study [6], and the Religious Orders Study and Memory and Aging Project (ROS/MAP) [7,8] have provided significant insight into potential links of vascular factors to dementia, including AD. An important risk factor for dementia includes lacunar and larger cerebral infarcts in the brain that are pathologic markers of clinical or subclinical stroke [9–11]. Others have subsequently shown that ischemic brain injury, commonly detected in pathology as macro- and microinfarcts and vessel disease, e.g. atherosclerosis, arteriosclerosis, and cerebral amyloid angiopathy (CAA) (Table 1), are highly prevalent in older persons and are independent risk factors for cognitive dysfunction and dementia [6,12–17]. Over the past 50 years the control of vascular risk factors, especially hypertension, has led to a major decline in the annual risk of stroke. Whether improved control of vascular risk factors has translated to decreased dementia risk is not known but has been suggested [18].

The most common etiology of dementia in older persons includes both mixed vascular and AD pathologies that become even more common as aging increases as both vascular and AD pathologies accumulate over time [19,20]. For example, in the longitudinal ROS/MAP, over half of the individuals with AD had a combination of both AD and vascular pathologies [7,8]. Importantly, the deleterious effect of vascular pathologies combined with AD pathology leads to increased likelihood of dementia; this is true for both large infarcts (commonly manifested as stroke) and microinfarcts in individuals with similar levels of AD

Table 1
Brain vascular injuries and disease; Table 1 summarizes ascular tissue injury and vessel disease, based on pathology, microscopic visualization and radiographic description

| Vascular tissue injury | Pathologic size | Gross or microscopic visualization | Radiographic description |
|---|---|---|---|
| Macroinfarcts (also gross infarcts) | ~ ≥ 1 mm (random missing; ≥1 mm toward 5 mm) | Gross | ≥3 mm on conventional MRI imaging (3 mm to 15 mm lesion CSF-density with FLAIR-hyperintense rim defined as lacune of presumed vascular origin) [76] |
| Microinfarcts | 100 μm to 3 mm (missing based on sampling protocol; mean < 1 mm) | Microscopic | Mostly undetectable. Cortical microinfarcts 1–3 mm may be visible as FLAIR-hyperintense lesions [77], recent microinfarcts may be visible as DWI-hyperintense lesions. [72] |
| Primary intraparencymal hemorrhages | ≥5 mm | Gross | ≥5–10 mm |
| Microbleeds | ≤5 mm | Gross or microscopic | 2–10 mm on T2*-weighted MRI [76] |
| White matter hyperintensity of presumed vascular origin | NA | Gross or microscopic | Hyperintense on T2-weighted MRI [76] |
| Vessel disease | Affected vessel | Gross or microscopic visualization | Radiographic description |
| Atherosclerosis | Arteries | Gross (large/medium arteries) or microscopic (medium/small arteries) | Angiography<br>Vascular Doppler examination<br>Carotid intimal-media thickness |
| Arteriolosclerosis | Arterioles | Microscopic | Not directly visible |
| Cerebral Amyloid angiopathy | Arterioles<br>Arteries<br>Capillaries | Microscopic | Amyloid ligand imaging [78,79] |
| Blood Brain Barrier | Capillaries (as part of neurovascular unit) | Electron microscopy | Dynamic contrast-enhanced MRI [80] |

Abbreviations: MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted MRI.