Published in final edited form as:

Alzheimers Dement. 2015 June ; 11(6): 710–717. doi:10.1016/j.jalz.2014.10.008.

Vascular Contributions to Cognitive Impairment and Dementia Including Alzheimer's Disease

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Introduction

A recent scientific statement from the American Heart Association (AHA) and American Stroke Association (ASA) highlighted the significance of vascular contributions to cognitive impairment and dementia (1), coined "VCID" here and referred to as vascular dementia and/or vascular cognitive impairment and/or vascular contributions to dementia alternatively. The concept for 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 the Alzheimer's Disease-Related Dementia (ADRD) Summit. The ADRD Summit set research priorities for small vessel VCID research over the next 5–10 years: develop the next generation experimental models, encourage basic science investigation on the impact of AD risk factors on cerebrovascular function and vice versa (3, 4). The Alzheimer's Association, with scientific input from the NINDS and the National Heart, Lung and Blood Institute (NHLBI), convened a panel of cross-disciplinary experts in Chicago, IL, on December 17th, 2013 to determine the state of the science and to identify the needed step, including unanswered research questions, which will translate into improved clinical outcomes related to small vessel VCID. This manuscript summarizes the proceedings of this discussion.

State of the science

Decades of data, including landmark work of the Honolulu Asia Aging Study (HAAS), the Rotterdam Study (20), and the Religious Orders Study and Memory and Aging Project (ROS/MAP) (12, 13) have provided significant insight into potential links of vascular factors to dementia, such as AD. An important risk factor for dementia was the presence of lacunar and larger cerebral infarcts in the brain that are pathologic markers of clinical or subclinical stroke (5–7, 20). Others have subsequently shown that ischemic brain injury, commonly detected in pathology as macro- and micro- infarcts and vessel disease, e.g. atherosclerosis, arteriosclerosis, and cerebral amyloid angiopathy [CAA], are highly prevalent in older persons and are independent risk factors for cognitive dysfunction and dementia (17–23).

Mixed vascular and AD etiology dementia is one the common dementia in older persons, and becomes even more common as age increases as both vascular and AD pathologies accumulate over time (10)(11). For example, in the longitudinal ROS/MAP, over half of the individuals with AD had a combination of both AD and vascular pathologies (12, 13). 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 micro infarcts in individuals with similar levels of AD neuropathology (14, 15). Vascular lesions detected by imaging, in particular small vessel and microvascular white matter damage, typically detected in current clinical settings as type 2 hyperintensities on MRI, and also as leukoaraiosis detected by CT, are also highly prevalent in the elderly, and worsening is associated with cognitive decline (16). Addition of

either arteriosclerosis or atherosclerosis results in further increased likelihood of micro infarcts, and an even higher probability of dementia.

The plot thickens: Molecular and vascular mechanisms

Molecular mechanisms associated with the vasculature and with accumulating AD pathologies have been linked in several ways and may be linked to the increased neuronal death observed in the mixed etiology. Decreased blood flow prior to beta-amyloid (Aβ) deposition has been observed in the brain of both mouse models of AD and in individuals with AD, and has been proposed to contribute directly to the cognitive symptoms and, some studies suggest the changes in the vasculature impair clearance of Aβ, and thereby accelerate the progression of AD (60, 61)(62, 63). Adding to this picture is considerable evidence that type 2 diabetes mellitus (T2DM) and insulin resistance are linked to an increased risk of vascular disease, AD pathology, and dementia (24)(25)(26).

Molecular mechanisms that may be related have been further supported by recent genetic studies. The International Genomics of Alzheimer's Project (I-GAP), funded in part by the Alzheimer's Association, published a meta-analysis of data from nearly 75,000 individuals and identified 21 genetic risk loci for late-onset AD (LOAD)(31). Individuals with small vessel cerebrovascular disease were not excluded because it is integral with a large proportion of AD, as discussed above. However, pathologic analysis of a subset of I-GAP individuals enabled comparison of the odds ratio (OR) for AD dementia for each of the genetic loci based on clinical diagnosis alone, clinical plus standard pathological definition (plaques and tangles), or more criteria that take into account vascular pathology. Interestingly, for individuals with vascular lesions the OR of specific genetic loci were different, increased or decreased, versus OR calculated using "pure" AD-pathology subjects, suggesting that some loci may function and respond differently with respect to vascular vs. AD-specific (i.e. plaques and tangles) pathology. Further investigation is needed to understand the linkage of underlying mechanisms with these pathological changes.

The innate immune system has also been implicated as a potential connection point between AD and vascular disease. Innate immunity is activated both in cerebrovascular disease (34) and in AD, in which postmortem studies show chronic inflammation characterized by an influx of activated microglia and infiltrating monocytes around plaques and tangles (32). Lue and colleagues reported that plaques and tangles appear only to cause neurodegeneration when inflammation is also present (33). While it is unclear whether recruitment of the innate immune system is a response to damage or pathogenic in nature, large GWAS studies suggest innate immune cells, including resident microglia and infiltrating monocytes and may drive AD pathogenesis through vascular related mechanisms that we are just beginning to understand (35) (36). A potential linkage between the immune infiltration and VCID may be the disruption of the blood brain barrier (BBB), demonstrated in post-mortem brain tissue studies of individuals with AD-related cognitive impairment, although the mechanism and timing has been unclear (41–45)(46).

The brain is the most lipid rich organ in the body and has a specialized system to carry fats; several lines of evidence suggest that lipid and lipoprotein metabolism may provide key

insight into VCID and AD. Lipid metabolism has long been implicated in AD; *APOE* is both a known genetic risk factor for late onset AD and is a primary lipid carrier in the brain (37). ApoE4, the product of the detrimental *APOE* allele, has multiple neuropathological effects in the central nervous system, including a loss of cerebrovascular integrity and breakdown of the BBB (38). Mechanistically, the proinflammatory cyclophylin A (CypA)-matrix metalloproteinase-9 (MMP-9) pathway is activated in pericytes in transgenic humanized *APOE4* knock-in mice, leading to degradation of endothelial tight junctions as well as basement membrane proteins, and thus disruption of the BBB (39). Consistent with findings in transgenic *APOE4* mice, a recent study in cognitively normal humans found age-dependent BBB breakdown in *APOE4* carriers vs. non-*APOE4* carriers, as indicated by an increased CSF/plasma albumin ratio and increased CypA and MMP-9 levels in the CSF (40). Irrespective of mechanism, BBB disruption exposes the brain parenchyma to potentially neurotoxic blood proteins, e.g. thrombin, fibrin, plasmin and hemoglobin, as well as the iron from lysed erythrocytes (i.e., siderosis)(47).

The cholesterol transporter ABCA1 delivers lipids to ApoE as well as ApoA-I, the primary protein component of HDL (“good cholesterol”). ApoE and ApoA-I in turn transport cholesterol from organs and arterial walls to the liver for excretion (49). In *ABCA1* deficient mice, ApoE particles in the blood cannot become lipidated, ultimately resulting in increased amyloid burden in the dentate gyrus; conversely, in mice that overexpress *ABCA*1, this amyloid burden is nearly eliminated. Thus, drug discovery programs are looking for ways to increase *ABCA1* expression, for example by using Liver X Receptor or LXR agonists (50). Like ApoE, ApoAI may also play an important role in vascular contributions to brain health, as indicated by studies of *APOA-I/APOA-I* knockout mice crossed with the Amyloid Precursor Protein (APP)/PS1ΔE9 transgenic AD mouse model (48) (51). As ApoA-I and high density lipoprotein (HDL) protect endothelial function in large peripheral vessels (52), HDL appears to also promote endothelial repair in healthy subjects (54, 55); to affect activity of the innate immune system; to have anti-inflammatory and antioxidant functions (52, 54) (53). Taken together, understanding the roles of ApoA-I and HDL in neurovascular physiology is an important priority.

Cerebral pial collateral circulation has a special role in limiting damage due to cerebrovascular occlusion. The adverse hemodynamic environment present in the pia limits collateral circulation under normal condition, but when brain circulation is compromised, e.g. in an ischemic event, these pial collaterals can facilitate compensatory blood perfusion in brain regions that would otherwise be (even more) compromised. Genetic and environmental factors can combine to limit the anatomical extent and capacity of pial collaterals for compensatory circulation, and thus significantly increase severity of brain injury in occlusive vascular disease (56, 57). For example, aging causes rarefaction of collateral vessels associated with dysfunctional nitric oxide synthase signaling and increased collateral tortuosity and resistance, increasing severity of ischemic injury (58), and genetic variation has been shown to influence and limit the extent of compensatory collateral circulation (59).

An emerging area of interest in cerebrovascular circulation in health and disease that may help identify novel drug targets is clearance of parenchymal waste, including Aβ, into the

CSF via perivascular circulation [also referred to as the glymphatic system (65, 66)]. Xie and colleagues demonstrated glymphatic Aβ clearance occurs during sleep (67), correlating with findings that both AD and VCID are linked to sleep disturbances (68). In addition to this potential role for the glymphatic system, BBB transport of Aβ from the parenchyma directly into vascular circulation is severely compromised in transgenic AD mouse models, and is a significant area for potential therapeutic development (69, 70). In the vasculature itself, another emerging topic with novel potential for intervention is stalled blood flow in brain capillaries due to leukocyte adherence to the endothelial lumen wall (64). When leukocytes adhere to the endothelium due to inflammation, only a small number of affected capillaries in the brain can result in significant decreases in downstream blood flow (64).

Animal models as a research tool

The VCID field has a need to model vascular factors, both genetic and non-genetic, to create novel models of mixed dementia representing the human disorder, in particular, for the purposes here, small vessel VCID. Several types of vascular models are currently used to study how vascular disease ay contributes to dementia: middle cerebral artery occlusion (MCAO) mouse model of stroke (71)(72); the bilateral common carotid stenosis (BCAS) model that creates chronic cerebral hypoperfusion (73); several mutant APP transgenic mice that develop CAA and CAA-related cerebrovascular deficits in addition to classic parenchymal Aβ pathology (74); and, finally, the Dutch APP mutation mouse model of CAA that develops extensive vascular Aβ deposits at an advanced age, but develop very few parenchymal Aβ plaques (75). There is also a more aggressive mouse model of CAA that includes Aβ accumulation in the vessel wall (76). Rosenberg and colleagues developed Another potential model are rats fed the Japanese Permissive Diet (JPD) of low protein and high salt, as they develop spontaneous hypertensive/stroke (SHR/SP) with unilateral carotid occlusion and white matter damage that evolves over weeks to months (77).

Yet another model of cardiovascular disease, wild type mice fed a diet deficient in B6, B12 and folic acid to drive a condition of hyperhomocysteinemia, which is implicated as a potential risk factor for cardiovascular disease, stroke, T2DM, vascular dementia, and AD (78). Feeding this diet to a transgenic mouse overexpressing APP resulted in an induction of a proinflammatory state and a change in the distribution of amyloid. Further, these mice have cognitive impairments and an increased number of microhemorrhages. Hypertensive animal models, such as those that display white matter disease, may also be useful, since a major risk factor for cerebrovascular disease is hypertension. In this regard, one example of a mouse model already used for systemic vascular and cardiac research, that may be useful for better understanding VCID, overexpresses renin under an albumin promoter develops an allele-dose-dependent hypertension, heart failure and loss of collaterals in the hetero- and homozygous strains (79). Despite the utilization of these models, there is lack of clear animal model(s) to tease out the role of VCID (such as associated risk factors) in dementia onset and progression. As discussed in the below section, the need for new model systems with metabolic similarity to humans, such as animal models with white matter vascular injury, animal models of hypertension or the potential utility of stem cell/induced pluripotent models are in need of further exploration.

Biomarkers of VCID

Biomarkers that precede and predict onset and that demonstrate the level of burden and track progression of small vessel disease-related brain injuries are the gold standard for the scientific community, and such a biomarker would greatly enhance the development of interventions for VCID with the greatest impact on AD and the associated high disease burden of related mixed dementias with a vascular component. Today, subsets of such biomarkers are in early development in clinical research with the ultimate goal of transferring to a clinical setting, and there is still much unknown about the longitudinal changes associated with VCID that may inform biomarker discovery. Tools such as diffusion-weighted magnetic resonance imaging (DWI-MRI) sequences to characterize acute/sub-acute microinfarcts (82) and functional MRI (fMRI) to assess impaired vascular reactivity associated with CAA (83) are being explored. Another area of exploration, a CAA-specific amyloid PET imaging tracer may be useful for diagnosing CAA before symptoms become apparent, quantifying CAA burden at the time of symptom presentation, monitoring CAA progression over time, and/or assessing response to a CAA-directed treatment. During investigation of CAA in mouse models, Zipfel and colleagues identified a fluorescent phenoxazine analog called resorufin that preferentially binds to CAA rather than parenchymal Aβ (80), and are now working to develop second-generation analogs to overcome challenges associated with affinity and solubility. Such tools may provide insight into VCID related changes and possible information on the longitudinal progression of these changes. Possible other areas of exploration for potential biomarkers may include measures related to microinfarcts, microbleeds, siderosis, white matter lesions, microinfarcts, altered microstructure, BBB breakdown and pericyte degeneration (shown to play a critical role in animal models of AD) (81), endothelial activation, as well as various aspects of immune dysfunction and inflammation, blood flow reductions, and vascular compliance. A greater understanding of the biological underpinnings discussed above will significantly inform the development of novel and informative biomarkers related to VCID.

Summary and next steps

One of the key concepts to emerge from this meeting is the recognition that cerebrovascular disease and especially small vessel disease is common in aging, and does not typically occur in isolation, but rather is associated with AD. Further there is a broad spectrum of comorbid conditions that commonly co-exist with AD and related dementia, including hypertension, diabetes, hypercholesterolemia, obesity, low physical activity, depression, and smoking. In discussion about how to move the field forward, meeting participants identified two focus areas: 1) the need to identify and understand the molecular and cellular mechanisms and targets that underlie the contribution of vascular disease to AD and dementia; and 2) the need to facilitate development and validation of non-invasive biomarkers of key vascular processes related to cognitive and neurologic impairment. For both of these goals, it is clear that new research tools are needed, including innovative technical approaches to imaging and fluid-based clinical research, and biological tools including humanized animal models, including animal models with metabolic similarity to humans, animal models with white matter vascular injury, animal models of hypertension; and the potential utility of stem cell/induced pluripotent models. Tools are needed to answer gaps identified during this meeting:

- Lipid metabolism and its role in amyloid deposition and cognitive/behavioral change
- Various roles of different cell types of the innate and adaptive immune systems
- Vascular injury and the response to injury
- Mechanisms for brain blood flow decrease in AD and other dementias
- The role of small vessel disease and blood-brain barrier breakdown
- Effects of reduced blood flow and changes in blood pressure
- Role of and interactions with other risk factors such as diabetes, including study of the pre-diabetic brain without the confounding effects of treatment
- Genetic cross-talk between the vasculature and the brain
- Studies of mixed etiology AD dementia

Novel biomarkers are also needed both for investigation of basic science research questions and to be developed as potential clinical disease markers. These markers need to be validated at an early stage in humans to ensure applicability for human studies:

- Better markers of blood flow, particularly for cerebral small vessels and collateral circulation
- A CAA-specific or other imaging compound that recognizes beta-amyloid or other markers, specifically and selectively in the cerebrovasculature
- Markers that enable more precise assessment of where pathology occurs in the brain parenchyma and blood vessels and the quantitative distribution of pathology
- Biomarkers that detect breakdown or dysfunction of blood-brain barrier permeability
- Biomarkers that reflect damage to brain structure and connectivity caused by microinfarcts, which are largely undetectable to current neuroimaging
- Vascular biomarkers of AD/dementia risk in prediabetic and insulin-resistant adults
- Improved imaging markers of cerebral vascular dysfunction
- Markers of peripheral circulatory system components that contribute to neuroinflammation.
- Improved outcome measures and clinical diagnostic criteria that accurately reflect the range of vascular events that impact cognition.

The mobilization of such studies will require significant investments at the federal and international levels, with targeted requests for proposals (RFAs) and funding calls. To help initiate global commitment of both the funding and the scientific communities, the Alzheimer’s Association launched a targeted grant program to fund pilot investigations for further discovery, and ultimately, motivate increased new investment by the international scientific funding communities into the VCID area of study.

Future investments for these areas of scientific discovery will be essential to galvanize the scientific community and provide forums of communication between the dementia and vascular fields. As a next step, focused research sessions and presentations are at various stages of planning for annual AD, dementia and cardiovascular focused conferences, including the Alzheimer's Association International Conference (AAIC) and two American Heart Association (AHA) conferences, including Atertiosclerosis, Thrombosis, and Vascular Biology (ATVB) 2014 and the AHA Scientific Sessions 2014. There is a clear need to both convene cross-disciplinary dialogues of the vascular and dementia communities and provide opportunities of global investment toward the ultimate goal of successful vascular intervention to decrease the burden of AD and other dementias

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Table 1

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