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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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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 Vascular Doppler examination Carotid intimal-media thickness
Arteriolosclerosis	Arterioles	Microscopic	Not directly visible
Cerebral Amyloid angiopathy	Arterioles Arteries 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.

neuropathology [21,22]. Vascular lesions detected by imaging, particularly small vessel and microvascular white matter damage, that are typically detected in current clinical settings as type 2 hyperintensities on magnetic resonance imaging (MRI), and also as leukoaraiosis detected by CT, are also highly prevalent in the elderly, and worsening is associated with cognitive decline [12,23]. Addition of either arteriosclerosis or atherosclerosis results in further increased likelihood of microinfarcts, and an even higher probability of dementia.

3. The plot thickens: molecular and vascular mechanisms

Molecular mechanisms associated with both vascular and AD pathologies have been linked in several ways and may act synergistically to increase the likelihood of neuronal death observed in mixed etiology. Decreased blood flow before 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 [6,13–15]. 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 [16,17,24]. However, the picture is far from clear as there has also been evidence to the contrary [25].

Recent genetic studies provide further support for VCID. 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 [26]. Individuals with small vessel cerebrovascular disease were not excluded because it is integral with a large proportion of AD, as discussed previously. 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 additional criteria that take into account vascular pathology. Interestingly, for individuals included in I-GAP with vascular lesions the OR of specific genetic loci were different (either increased or decreased) compared with the OR calculated using individuals with "pure" AD-pathology. This key finding suggests some loci may function and respond differently with respect to vascular vs. traditional AD (i.e. plaques and tangles) pathology and set the stage for needed further investigation to understand the linkage of underlying mechanisms with both pathological and cognitive changes.

The innate immune system has long been implicated as a potential connection point between AD and vascular disease. Innate immunity is activated both in cerebrovascular disease [27] and in AD, in which postmortem studies show chronic inflammation characterized by an influx of activated microglia and infiltrating monocytes around plaques and tangles [28]. Lue and colleagues reported that plaques and tangles appear only to cause neurodegeneration when inflammation is also present [29]. While it is unclear whether the recruitment of the innate immune system is a response to damage or pathogenic in nature, large genome-wide association study (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 [30,31]. A potential intersection point between immune infiltration and VCID may be the disruption of the blood brain barrier (BBB), which is commonly demonstrated in post-mortem brain tissue studies of individuals with AD-related cognitive impairment, although the mechanism and timing of BBB dysfunction during pathogenesis remains unclear [32–37].

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 the primary lipid carrier in the brain [38]. ApoE4, the product of the detrimental *APOE* ε4 allele, has multiple neuropathological effects in the central nervous system, including impaired clearance of Aβ and contributing to a loss of cerebrovascular integrity and breakdown of the BBB [39]. Mechanistically, the proinflammatory cyclophylin A (CypA)-matrix metalloproteinase-9 (MMP-9) pathway is activated in pericytes in transgenic humanized *APOE* ε4 knock-in mice, leading to degradation of endothelial tight junctions and basement membrane proteins, and thus disruption of the BBB [40]. Consistent with findings in transgenic *APOE* ε4 mice, a recent study in cognitively normal humans found age-dependent BBB breakdown in *APOE* ε4 carriers vs. non-*APOE* ε4 carriers, as indicated by an increased cerebrospinal fluid (CSF)/plasma albumin ratio and increased CypA and MMP-9 levels in the CSF [41]. Irrespective of mechanism, BBB disruption exposes the brain parenchyma to potentially neurotoxic blood proteins, e.g. thrombin, fibrin, plasmin, and hemoglobin, and the iron from lysed erythrocytes (i.e., siderosis) [42].

The cholesterol transporter ABCA1 delivers lipids to ApoE and ApoA-I, the primary protein component of plasma high density lipoprotein (HDL; "good cholesterol"). ApoE and ApoA-I in turn transport cholesterol from organs and arterial walls to the liver for excretion [43]. In *ABCA1* deficient mice, ApoE particles in the brain cannot become lipidated, ultimately resulting in increased amyloid burden in the dentate gyrus; conversely, in mice that overexpress *ABCA*1 in brain, amyloid burden is nearly eliminated [44]. Thus, several drug discovery programs are seeking to increase *ABCA1* expression, for example by using liver X receptor agonists [45]. 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 or

apoA-I transgenic mice crossed with the amyloid precursor protein (APP)/PS1ΔE9 transgenic AD mouse model, where decreased amyloid load and improved cognitive performance are directly correlated with ApoA-I abundance [46,47]. ApoA-I and HDL are well established to protect endothelial function and promote endothelial repair in large peripheral vessels [48–50], and are also reported to affect activity of the innate immune system and provide anti-inflammatory and antioxidant functions [48,49,51]. 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 [52,53]. For example, aging causes the rarefaction of collateral vessels associated with dysfunctional nitric oxide synthase signaling and increased collateral tortuosity and resistance, increasing the severity of ischemic injury [54], and genetic variation has been shown to influence and limit the extent of compensatory collateral circulation [55].

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 [56,57]). Xie and colleagues demonstrated glymphatic Aβ clearance occurs during sleep [58], correlating with findings that both AD and VCID are linked to sleep disturbances [59]. 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 [60,61]. 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 [62]. 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 [62].

4. Animal models as a research tool

The VCID field needs to incorporate vascular factors, both genetic and nongenetic, to create novel models of mixed dementia that are truly representative of 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 contributes to dementia: middle cerebral artery occlusion mouse model of stroke [63,64]; the bilateral common carotid stenosis model that creates chronic cerebral hypoperfusion [65]; several mutant APP transgenic mice that develop CAA and CAA-related cerebrovascular deficits in addition to classic parenchymal Aβ pathology [66]; 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 [67]. There is also a more aggressive mouse model of CAA that includes Aβ accumulation in the vessel wall [68]. Another potential model where rats are fed the Japanese Permissive Diet of low protein and high salt, they develop spontaneous hypertensive/stroke with unilateral carotid occlusion and white matter damage that evolves over weeks to months [69].

In yet another model of cardiovascular disease, wild type mice fed a diet deficient in B6, B12, and folic acid develop hyperhomocysteinemia, which is implicated as a potential risk factor for cardiovascular disease, stroke, T2DM, vascular dementia, and AD [70]. Feeding this diet to a transgenic mouse overexpressing APP induced a proinflammatory state and a change in the distribution of amyloid. Furthermore, 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, because 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 and develops allele dose-dependent hypertension, heart failure, and loss of collaterals in the hetero- and homozygous strains [71]. Despite the utilization of these models, the field still lacks 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 later 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.

5. 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. Such a biomarker (or group of biomarkers) 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 MRI (DWI-MRI) sequences to characterize acute/subacute microinfarcts [72] and functional MRI to assess impaired vascular reactivity associated with CAA [73] are being explored. Another area of exploration, such as a CAA-specific amyloid PET imaging tracer may be useful for diagnosing CAA before clinical 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 [74], and are now working to develop second-generation analogs to overcome challenges associated with affinity and solubility to ultimately yield a PET ligand for suitable clinical use. Such tools may provide insight into VCID related changes and possible information on the longitudinal progression of these changes. Additional areas of exploration for potential biomarkers include measures related to microinfarcts, microbleeds, siderosis, white matter lesions, microinfarcts, altered microstructure, BBB breakdown, cerebrovascular endothelial dysfunction, and pericyte degeneration (shown to play a critical role in animal models of AD) [75], and 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.

6. Summary and next steps

One of the key concepts to emerge from this meeting is the recognition that cerebrovascular disease, particularly the small vessel disease that is common in aging, does not typically occur in isolation, and is often associated with AD and especially with cognitive decline. Further there is a broad spectrum of other comorbid conditions that commonly coexist 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 noninvasive 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, animal models with metabolic fidelity to humans, animal models with white matter vascular injury, animal models of hypertension; and the potential utility of stem cell/induced pluripotent or additional in vitro models engineered to mimic the neurovascular unit. 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 underlying 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 prediabetic brain without the confounding effects of treatment.
- Genetic cross-talk between the vasculature and the brain.
- Studies of mixed etiology AD dementia.
- Effects of interventions to control vascular risk factors on cognition.

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 and determine the effects of vascular risk factor control on cognition.

The mobilization of such studies will require significant and targeted investment at the national and international levels. To help initiate the 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 investment 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; two AHA conferences, including Atertiosclerosis, Thrombosis, and Vascular Biology 2014 and the AHA Scientific Sessions 2014; and the NIH-sponsored Workshop on Small Blood Vessel Biology and Disease. 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.

RESEARCH IN CONTEXT

1. Systematic review: Significant research is ongoing to better understand vascular contributions to cognitive impairment and dementia. In December 2013, the Alzheimer's Association, with scientific input from National Institute of Neurological Disorders and Stroke and National Heart, Lung and Blood Institute, convened experts from around the world to focus on how vascular factors contribute to Alzheimer's disease and related dementia. This manuscript summarizes the meeting and the resultant discussion.
2. Interpretation: One of the key concepts to emerge is the recognition that cerebrovascular disease, particularly small vessel disease, does not typically occur in isolation, and is often associated with cognitive decline.
3. Future directions: In discussion about how to move the field forward, meeting participants identified: (1) the need to identify and understand molecular and cellular mechanisms and targets underlying the contribution of vascular disease to Alzheimer's and dementia; and (2) the need to facilitate development and validation of noninvasive biomarkers of key vascular processes related to cognitive and neurologic impairment.

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