Alzheimer’s and cerebrovascular disease: the twin towers of dementia

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ABSTRACT

With dementia prevalence on the rise, it is imperative to develop novel therapies and treatments to address the increasing recognition of the clinical and pathological overlap of Alzheimer’s and cerebrovascular disease - the top two leading causes of dementia. Although the research methods currently employed have made great advances towards our understanding of comorbid neurovascular and neurodegenerative diseases, these knowledge-based silos have had a tendency to operate in relative isolation. As our cumulative body of knowledge within each platform increases, so should the coordination of research. By examining current findings in neuroimaging, neuropsychology, genetics, neuropathology, and molecular neurobiology, this blanket-level mini-review will examine the spectrum of research findings that contributes to our understanding of Alzheimer’s and vascular contributions to dementia.

Introduction

Given our aging population, dementia was recently recognized by the World Health Organization as a public health priority. With Alzheimer’s disease (AD) and vascular dementia (VaD) as the top two leading causes of dementia, the need to develop novel treatment targets and more aggressive management strategies has never been greater. Although AD and VaD frequently co-occur and share common risk factors, they present and progress heterogeneously, encompassing a broad range of complex neurovascular and neurodegenerative pathological processes and etiologies. Recent advances in neuroimaging, neuropsychology, genetics, neuropathology, and molecular neurobiology have led to the development of promising early biomarkers that have improved the diagnosis and prognostication of these co-contributors to dementia. However, despite these advances, research efforts often face challenges in bridging the interdisciplinary divide, often acting independently within cultural silos. To overcome these knowledge-translation obstacles the identification of future treatment targets may arise more effectively if our efforts turn towards the synthesis of findings across these knowledge platforms.

Neuroimaging

Advances in MRI segmentation techniques have yielded numerous useful biomarkers for measuring neurodegenerative and neurovascular burden in clinical and normal populations. The various combinations of these markers suggest that the vascular contributions to cognitive decline and AD neuropathology may be more closely related than previously thought. For example, the well-established AD markers of hippocampal volume1 and global atrophy were also recently acknowledged as significant MRI correlates of the cognitive dysfunctions outlined by the National Institute of Neurological Disorders and Stroke-Canadian Stroke...
Network (NINDS-CSN) for vascular cognitive impairment. Additionally, recent findings suggest that small vessel disease, manifested as white matter hyperintensities of presumed vascular origin (WMH), can interact with beta amyloid (Aβ) pathology to negatively impact hippocampal volume in non-demented elderly. A similar association with hippocampal atrophy was also demonstrated in AD patients with cholinergic hyperintensities, an interesting relationship as cholinesterase deficits have also been demonstrated in VaD independent of concomitant AD pathology. Advances in cortical thickness measurement that led to the identification of a cortical signature for AD have also yielded findings which suggest that vascular risk factors and WMH may also influence cortical thinning in AD and MCI signature regions, where watershed regions of vascular supply and rich club hubs of functional connectivity coincide. Indeed, recent attention regarding the presence of WMH and lacunar infarcts in AD and MCI clinical populations have led numerous international groups to acknowledge vasculopathy as a core feature that needs to be addressed if we are to move forward with the improvement of clinical outcomes in dementia.

Although WMH and lacunar infarcts are the most commonly correlated markers of small vessel disease, measurements of other MRI-based small vessel disease markers have gained some recent attention. As differential markers commonly associated with hypertensive arteriopathy and cerebral amyloid angiopathy (CAA), MRI-visible perivascular spaces (PVS), superficial siderosis, and cortical microinfarcts are commonly assessed using visual rating scales; although some recent progress has been shown towards the automatic segmentation PVS. Given the significant overlap between CAA and AD, as well as the increased risk for stroke and intracerebral hemorrhage, the importance of cerebral microbleeds and superficial siderosis has justifiably garnered significant attention. Moreover, the modified Boston criteria for the clinicoradiological diagnosis of sporadic possible/probable CAA is partially based on the burden of lobar microbleeds and superficial siderosis observed on MRI.

Moving beyond basic structural imaging markers, advanced neuroimaging techniques have also yielded novel findings that inform us on the overlap between neurodegenerative and neurovascular burden in clinical and elderly populations. Diffusion tensor imaging (DTI), an MRI-based measure of white matter structural integrity, is increasingly being utilized in combination with markers of white matter small vessel disease burden and focal gray matter atrophy to assess structural and functional brain networks observed in cognitive impairment and AD. Recently described as a cascading network failure in AD progression, assessment of vascular disruptions along specific white matter tracts of the default mode network involves the use of ‘task-free’ functional MRI (fMRI), often in combination with structural imaging metrics. Blood perfusion changes assessed by single photon emission computed tomography (SPECT), dynamic susceptibility contrast, and more recently, non-invasive arterial spin labelling (ASL) MRI, have also produced findings that further confirm the cerebral hypoperfusion and microvascular disease observed in AD. Moreover, changes in the blood oxygen level-dependent (BOLD) signal in response to changes in end-tidal partial pressure of carbon dioxide (P\textsubscript{ET\textsubscript{CO\textsubscript{2}}}) as a vasoactive stimulus has been used to assess cerebrovascular reactivity (CVR), providing additional insight to the progression of small vessel disease in dementia. Additionally, although still relatively understudied, as a literal ‘eye’ into the underlying Aβ, tauopathy, and vascular burden observed in the brain, recent findings have proposed the use of ocular and retinal abnormalities as novel non-invasive biomarkers in the study of AD and cerebrovascular disease.

Genetics

Moreover, many of these studies have included analyses that examine the associations between these imaging biomarkers and the presence of the apolipoprotein E epsilon 4 (APOE4) allele on chromosome 19, a strong genetic marker of AD, which has recently been implicated to influence poor gait, post-stroke cognitive decline, and VaD. Large scale genome wide association studies (GWAS) analysis on 74,046 individuals of European ancestry have identified at least 20 loci (including APOE) associated with late-onset AD, although several rare genetic variants not detected by GWAS have also been suggested. Genome wide meta-analyses of small vessel disease, stroke, and their shared genetic contributions with AD have also reported significant findings; however, a full understanding of these genetic associations, the underlying mechanisms they represent, and how this information translates into therapeutic advances is still underway.

Neuropathology

Several autopsy studies also report on the common comorbidity between cerebrovascular disease and AD pathology, with some studies suggesting that vascular pathology may lower the threshold for dementia. Further analyses suggest several pathophysiological mechanisms including atherosclerosis in the Circle of Willis, arteriosclerosis, blood brain barrier dysfunction, pericyte loss, hypoperfusion, clasmatodendrosis, and venous collagenesis. Moreover, the common overlap of CAA and AD has been reported in several postmortem studies, with one study combining two different longitudinal clinicopathological studies reporting CAA to be commonly (present in 79% of all cases) associated with...
increased odds of AD dementia and an increased rate of decline in global cognition, perceptual speed, episodic and semantic memory.

**Molecular Neurobiology**

Finally, recent attention has focused on understanding the systems of the brain which are responsible for fluid circulation and the clearance of waste and neurotoxic proteins, such as the Aβ, α-synuclein, and hyperphosphorylated tau within neurofibrillary tangles, found in AD and other dementia pathologies. Of particular interest is the lymphatic system, a complex system of perivascular tunnels surrounding cerebral veins and arteries, where parenchymal waste and interstitial solute clearance is primarily driven by the astroglial water channel aquaporin-4. Interestingly, preclinical models have demonstrated that the lymphatic system is primarily engaged during sleep, suggesting that poor sleep may be associated with poor waste clearance, which was recently supported by a small proof-of-concept study on cerebrovascular disease patients using MRI-visible perivascular spaces and polysomnography-derived sleep parameters.

Parallel research based around the concept of protein elimination failure angiopathy (PEFA) in CAA and AD focuses on a cerebral waste clearance system driven by physiological functions around vascular basement membrane pathways. Recent experiments using biotinylated and fluorescent Aβ injected into the hippocampus and tracers injected into the cerebrospinal fluid of mice suggest several basement membrane layer clearance pathways, possibly influenced by size, rigidity, and charge (positive/negative/neutral) of the particles being transported.

**Conclusion**

As evidenced by this blanket-level mini-review of the findings from clinical, neuroimaging, genetics, pathology, and basic science research, it is hopefully evident that 100 more papers correlating WMH with another cognitive test will no longer be sufficient to contribute to our understanding of the overlap between neurovascular and neurodegenerative disease. While there are some gaps within each of these knowledge-based platforms, it would also be important to consider bridging the interdisciplinary gaps between them as well. In order to provide a more comprehensive understanding of the complex neurological disease processes resulting in dementia, future work should focus on international research collaborations with multi-modal, multi-platform, big data analytics. As a scientific community, we are now at a stage where effective progress towards therapeutic advances will likely arise from the analysis of progression data synthesized from numerous interdisciplinary platforms.

**Acknowledgements & Funding**

We gratefully acknowledge financial and salary support (JR, MFH, FG) from the Canadian Institutes of Health Research (#125740 & #13129), Heart & Stroke Foundation Canadian Partnership for Stroke Recovery, Hurvitz Brain Sciences Research program at Sunnybrook Research Institute and the Linda C. Campbell Foundation. JR additionally received partial funding from the Canadian Vascular Network and the Ontario Brain Institute’s Ontario Neurodegenerative Disease Research Initiative. Furthermore, we would like to graciously thank the Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Dept. of Medicine, and the Brill Chair in Neurology, SHSC and Dept. of Medicine, University of Toronto for financial and salary support (SEB). Finally, we would like to thank Sabrina Adamo (Junior Imaging Analyst, Sunnybrook Research Institute) for her assistance with the literature review.

**Conflict of Interest**

JR, MFH and FG report no conflicts of interest. SEB reports institutional grants from GE Healthcare, Transition Therapeutics, Cognoptix, and Biogen Idec.

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