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Perspective

Multiple neuropathologies and dementia in the aging brain: A key role for cerebrovascular disease?

Andreas Charidimou, Anand Viswanathan*

Hemorrhagic Stroke Research Program, JPK Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Abstract This short perspective discusses the conclusions of a Research Roundtable meeting held in October in 2014 within the overall theme of understanding the role of additional/comorbid pathologies in the aging brain and their potential interaction with clinical Alzheimer's disease and other dementia phenotypes. We specifically examine the key role of for cerebrovascular small vessel disease in this context and highlight future directions.

Keywords: Dementia; Alzheimer's disease; Cerebral small vessel disease; Stroke; Aging

Several lines of research have revealed that multiple overlapping pathologic processes in the aging brain contribute to dementia, including Alzheimer's disease dementia [1]. This pathophysiological complexity creates significant controversies in clinicopathologic correlations of the underlying causes of dementia and has implications in identifying potential targets for disease modification. The recent perspective article by Rabinovici et al. [2] summarizes important presentations made at Research Roundtable meeting October in 2014 within the overall theme of understanding the role of additional/comorbid pathologies in the aging brain and their potential interaction with clinical Alzheimer's disease and other dementia phenotypes. On the basis of a systematic review of the relevant literature the article postulates that indeed dementia syndromes are much more commonly related to multiple neuropathologies especially in older individuals, rather than a single underlying process [2]. Going one step further, the roundtable participants explore how mixed pathologies should influence the design of clinical trials and drug development in dementia. In summary, the authors suggest that a better understanding of the complexity of clinical and neuropathologic phenotypes is urgently needed. This knowledge could be then translated and integrated into biochemical and neuroimaging candidate biomarkers that will better detect multiple pathologies and enable better-targeted therapeutic developments in the field [2].

The topic is indeed highly complex. The complexity stems not only for comorbid neurodegenerative pathologies in the setting for Alzheimer's disease (rigorously discussed in the article), but also from concomitant cerebrovascular pathologies. This latter aspect might deserve another roundtable meeting to be defined and deserves some more thorough discussion in the context of dementia trials. Cerebrovascular disease is highly prevalent in the elderly brain [3]. However, the impact of these lesions on dementia, the prevalence of vascular dementia, and the pathophysiological pathways and implications behind characteristic in vivo imaging findings and ex vivo pathologic lesions are still under debate. Three types of pathologies affecting cerebral blood vessels can contribute to dementia: (1) atherosclerosis, (2) cerebral amyloid angiopathy, and (3) nonamyloid-related small vessel disease pathology, including lipohyalinosis and arteriolosclerosis [3,4]. These cerebrovascular pathologies can all lead to various downstream cerebrovascular lesions and associated focal and diffuse brain tissue injury, including large and small vessel infarcts, microinfarcts, microbleeds,

*Corresponding author. Tel.: 617 643 3876; Fax: 617 726 5346.
E-mail address: aviswanathan1@partners.org

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and white matter lesions. Of particular interest is the role of cerebral amyloid angiopathy, a well-defined entity, almost invariably present in Alzheimer's disease brains, that seems to affect the pathologic and clinical phenotype of dementia, including lowering the threshold for clinically overt dementia [5–7]. In a recent community-based autopsy study, cerebral amyloid angiopathy was found to be an important determinant of Alzheimer's disease dementia and decline in multiple cognitive domains in old age [1]. This effect was independent and over and above Alzheimer's disease pathology and other common age-related neuropathologies [1]. Similar findings were recently reported for cerebral atherosclerosis and arteriolosclerosis in the setting of Alzheimer's disease dementia [8].

Taken together, these and other observations support a key role for cerebral vessel pathologies in Alzheimer's disease dementia, but they might be under-recognized risk factors. An unmet need in fully elucidating the contribution of cerebrovascular pathologies is the lack of standardized criteria for their neuropathologic assessment (including related lesions) in human postmortem brains [3]. This lack of standardization is reflected in this roundtable perspective article [2], which nicely summarizes the pathologic staging of neurodegenerative pathologies, but a similar scheme for cerebrovascular pathologies (and the complexities to define these) was not identified and suggested.

The conclusions from this Research Roundtable meeting [2] will help to better inform clinical practice and future research trial design. In should be emphasized however, in the design of these future trials the role of vascular brain injury must be carefully considered [9]. Because cerebrovascular disease burden might be modifiable, the implications of aggressive treatment of vascular risk factors, especially hypertension (with clear definitions of blood pressure targets), in disease-modifying Alzheimer's disease trials may be important for the treatment effect. A pragmatic trial (as defined by the authors) might attempt to target both clinical Alzheimer's disease progression and future stroke [10], as these two outcomes interact to lower the threshold for dementia and neurologic dysfunction in elderly individuals. Thus, the extent to which vascular care and blood pressure-lowering interventions can reduce dementia in elderly patients is testable in future trials in the field [11]. Finally, clear criteria to identify robust biomarkers of cerebral small vessel disease are also an urgent priority and are the focus of a new multicenter National Institute of Health funded initiative (http://www.ninds.nih.gov/funding/funding_announcements/rfa/RFA-NS-16-020.htm). Redefining our approach to dementia by considering the role of multiple cerebral pathologies in the disease, rather than only focusing on a single underlying pathology is of critical importance. This approach will improve our understanding of the pathophysiology of dementia and eventually help us design effective therapies for this devastating disease.

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