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Alzheimer's & Dementia 9 (2013) 76–92

Alzheimer's & Dementia

Vascular disease and dementias: Paradigm shifts to drive research in new directions

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Abstract Vascular disease was once considered the principal cause of aging-related dementia. More recently, however, research emphasis has shifted to studies of progressive neurodegenerative disease processes, such as those giving rise to neuritic plaques, neurofibrillary tangles, and Lewy bodies. Although these studies have led to critical insights and potential therapeutic strategies, interest in the role of systemic and cerebrovascular disease mechanisms waned and has received relatively less attention and research support. Recent studies suggest that vascular disease mechanisms play an important role in the risk for aging-related cognitive decline and disorders. Vascular disease frequently coexists with cognitive decline in aging individuals, shares many risk factors with dementias considered to be of the "Alzheimer type," and is observed more frequently than expected in postmortem material from individuals manifesting "specific" disease stigmata, such as abundant plaques and tangles. Considerable difficulties have emerged in attempting to classify dementias as being related to vascular versus neurodegenerative causes, and several systems of criteria have been used. Despite multiple attempts, a lack of consensus remains regarding the optimal means of incorporating vascular disease into clinical diagnostic, neurocognitive, or neuropathologic classification schemes for dementias. We propose here an integrative, rather than a strictly taxonomic, approach to the study and elucidation of how vascular disease mechanisms contribute to the development of dementias. We argue that, instead of discriminating between, for example, "Alzheimer's disease," "vascular dementia," and other diseases, there is a greater need to focus clinical and research efforts on elucidating specific pathophysiologic mechanisms that contribute to dementia phenotypes and neuropathologic outcomes. We outline a multitiered strategy, beginning with clinical and public health interventions that can be implemented immediately, enhancements to ongoing longitudinal studies to increase their informative value, and new initiatives to capitalize on recent advances in systems biology and network medicine. This strategy will require funding from multiple public and private sources to support collaborative and interdisciplinary research efforts to take full advantage of these opportunities and realize their societal benefits.

Keywords: Dementia; Vascular; Cerebrovascular; Pathophysiology; Risk factors; Metabolic syndrome; Magnetic resonance imaging; White matter hyperintensities; Obesity; Hypertension; Insulin resistance; Dyslipidemia

1. Introduction

Improvements in public health and medical care during the 20th century led to substantial increases in life expectancy [1]. As a result, the principal causes of death have undergone a substantial shift from predominantly infectious

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doi:10.1016/j.jalz.2012.02.007

diseases to cardiovascular disease, cancers, and, increasingly, progressive neurodegenerative dementias [2]. With this increased longevity in industrialized societies, it has become clear that although some limited decline in certain cognitive functions with the aging process is almost universal, as many as half of all individuals living into their 80s and 90s undergo more severe cognitive and functional deterioration warranting a clinical syndrome diagnosis of dementia.

As the post–World War II "baby boom" generation now enters the vulnerable ages for dementia, increasing attention has been drawn to the medical and economic impact of dementias [3]. During this time, advances in scientific methodology and technological capabilities (brought about to a considerable extent by members of this same birth cohort) have greatly enhanced our ability to characterize the clinical and neuropathologic features of aging-associated cognitive disorders. In particular, the inventions of laboratory-based immunochemistry, molecular biology, and advanced microscopy as well as clinic-based magnetic resonance imaging, nuclear medicine imaging, and digital tomographic neuroimaging have revolutionized our understanding and diagnosis of brain diseases.

The principal disease processes leading to dementia in older adults can be broadly thought of as falling into 2 groups: (1) neurodegenerative processes occurring within brain tissue itself, and (2) vascular disease processes resulting in brain injury and dysfunction. The past half-century has seen dramatic growth in our understanding of neurodegenerative disease processes, most notably the processes underlying the formation of amyloid plaques and neurofibrillary tangles eponymously associated with Alzheimer's disease (AD). In contrast, our view of the role of vascular disease processes in dementias has undergone several swings in emphasis over this interval, during which vascular mechanisms became less intensively studied. This shift in emphasis is evident even from the titles of some review articles on "vascular dementia" (VaD), alluding to this condition as an "enigma" [4] and asking whether we are on a "dead-end road" [5].

In this article, we will present a strategic overview of this extensive literature, highlighting some of the key findings that changed prevailing views regarding the role of vascular mechanisms in dementias. We will also consider the sources of research funding for studies conducted to date, and identify areas where gaps in funding priorities currently exist. We will then propose an agenda for future research in this area, including recommended modifications to the current paradigms by which vascular contributions to dementia syndromes are conceptualized.

As the historical aspects and evolution of concepts leading up to the present analysis have been well covered in several recent review articles and book chapters [6–9], we will only briefly summarize key points and will not recapitulate this material here, except where necessary to illustrate salient concepts.

2. Historical context

The notion that vascular factors mediate age-related cognitive decline was the prevailing view of "senile dementia" until the 1960s [4,10]. Thus, the terms "arteriosclerotic dementia" and its lay counterpart "hardening of the arteries in the brain" were in common use. Although this concept is often associated with the work of Binswanger first published in 1894 [6,11], many of the pathologic features can be traced back to the work of the French neurologist Max Durand-Fardel in the 1840s (cited in Ref. [12]). Until the last part of the 20th century, the occurrence of neuritic plaques and neurofibrillary tangles, the hallmark lesions described by Alzheimer in his seminal article of 1907 [13], were considered to be rare findings in patients with dementia, and more closely associated with early-onset or "presenile" dementias.

The emphasis in dementia research shifted dramatically starting in the 1970s and 1980s, based on several sets of observations. These include (1) the discovery that plaques and tangles were more common in postmortem material from individuals with dementing illnesses than had previously been thought, and more frequently than in those dying without dementia [14,15]; (2) the findings of neurodegeneration and associated deficits in the cholinergic system in the brains of patients with dementia [16], coupled soon thereafter with the discovery that anticholinesterase drugs had some therapeutic benefit in dementias [17] (refer also to subsequent meta-analysis in Ref. [18]); and (3) the discovery of the principal molecular composition of plaques (i.e., abnormally folded amyloid peptides [19]) and tangles (i.e., hyperphosphorylated tau proteins [20,21]). With the recognition that cholinergic-enhancing drugs have, at best, a limited impact on the underlying neurodegenerative processes [22], and the emergent preeminence of the amyloid cascade hypothesis [23], treatment development efforts have been intensely focused on interrupting the mechanisms of amyloid plaque formation. Several agents designed to affect amyloid production or clearance have been and are being tested in clinical trials [24]; however, none of these trials has yet progressed to the stage of applying for approval by Food and Drug Administration or other regulatory agencies.

3. Current state of knowledge

3.1. What is VaD?

VaD is often said to be the second most common form of dementia after AD [4,25]; some authors have even suggested it is the most common form [26]. However, such statements, and the data on which they are based, are predicated on having a commonly accepted definition of this condition. In the case of dementia attributable to vascular causes, this is far from the case. In fact, considerable variability exists in the literature with regard to the estimated prevalence of VaD, with estimates as low as 0.03% to as high as 98% (refer to Jellinger's review in Ref. [4]). Most of the estimates range