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Featured Article

METACOHORTS for the study of vascular disease and its contribution to cognitive decline and neurodegeneration: An initiative of the Joint Programme for Neurodegenerative Disease Research

METACOHORTS Consortium[1,*]

Abstract Dementia is a global problem and major target for health care providers. Although up to 45% of cases are primarily or partly due to cerebrovascular disease, little is known of these mechanisms or treatments because most dementia research still focuses on pure Alzheimer's disease. An improved understanding of the vascular contributions to neurodegeneration and dementia, particularly by small vessel disease, is hampered by imprecise data, including the incidence and prevalence of symptomatic and clinically "silent" cerebrovascular disease, long-term outcomes (cognitive, stroke, or functional), and risk factors. New large collaborative studies with long follow-up are expensive and time consuming, yet substantial data to advance the field are available. In an initiative funded by the Joint Programme for Neurodegenerative Disease Research, 55 international experts surveyed and assessed available data, starting with European cohorts, to promote data sharing to advance understanding of how vascular disease affects brain structure and function, optimize methods for cerebrovascular disease in neurodegeneration research, and focus future research on gaps in knowledge. Here, we summarize the results and recommendations from this initiative. We identified data from over 90 studies, including over 660,000 participants, many being additional to neurodegeneration data initiatives. The enthusiastic response means that cohorts from North America, Australasia, and the Asia Pacific Region are included, creating a truly global, collaborative, data sharing platform, linked to major na-

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tional dementia initiatives. Furthermore, the revised World Health Organization International Classification of Diseases version 11 should facilitate recognition of vascular-related brain damage by creating one category for all cerebrovascular disease presentations and thus accelerate identification of targets for dementia prevention.

Keywords: Dementia; Cerebrovascular disease; Small vessel disease; Neurodegeneration, Cohorts, Survey

1. Introduction

Worldwide, nearly 36 million people are estimated to be living with dementia. This is expected to triple by 2050. Cerebrovascular disease causes up to 45% of all dementias alone or in conjunction with Alzheimer's disease (AD) [1,2]. Despite vascular risk factor reduction being an achievable target for public health intervention in many countries, and some recent evidence of success in preventing dementia [3], knowledge about vascular contributions to dementia remains modest.

Many studies, from the early 1990s onward [4], have demonstrated that cognitive impairment and dementia are both common and under-recognized after stroke [5]. The concept of "vascular cognitive impairment" was introduced in 1994 [6], covering a spectrum of cognitive impairment after stroke to cognitive impairment in association with otherwise asymptomatic cerebrovascular disease. The most common vascular contributor to dementia is cerebral small vessel disease (SVD) [7], a condition that affects perforating vessels, thence white and gray matter, and accelerates neurodegenerative processes. Vascular dementia reflects the global effects of vascular disease on the brain, not just of multiple individual infarcts. [8,9] It results in stroke, cognitive decline and dementia, plus neuropsychiatric symptoms, gait, balance [8,9], and continence problems [10], necessitating a larger framework for targeted, comprehensive studies [11].

In 2006, the National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network convened a multidisciplinary research group to recommend standards for the study of vascular cognitive impairment [11]. In 2013 the Alzheimer's Association convened an expert working group, which summarized the state of vascular cognitive impairment science and identified areas where new knowledge is needed [12]. However, despite strong and unanimous evidence for the major burden of vascular cognitive impairment on both patients and their caregivers [13], most dementia research largely overlooks vascular disease as a cause. In part, this reflects that clinicians and researchers working on dementia, stroke, physical, or psychiatric manifestations are still too often segregated. "Stroke" and "dementia" (both syndromes, not pathological diagnoses) present to different clinical specialists (Fig. 1); stroke specialists under-recognize the cognitive impact of stroke, whereas dementia specialists under-recognize vascular inputs to dementia pathophysiology. This separation also affects research and funding initiatives, for example, vascular disease was rarely mentioned in a report on 169 European studies considered relevant to neurodegenerative disease research [14]. Better diagnostic criteria for the different cognitive profiles of vascular and AD are also needed [15].

The recognition of an important role for cerebrovascular disease in dementia opens major therapeutic opportunities. Vascular risk factor reduction and stroke prevention may already be reducing dementia incidence [3,16]. Increased government and public concern about dementia, as well as better grouping of codes for different cerebrovascular disease presentations in the revised International Classification of Disease (ICD) codes version 11 (ICD-11, release 2018, http://www.who.int/classifications/icd/revision/en/), will help advance understanding of cerebrovascular disease and its impact on neurodegeneration.

Here, we report on an initiative funded by the JPND to promote efficient use of available data in which we identified information, relevant to vascular disease, available in different types of studies that could provide large, statistically robust, generalizable data sets, and create platforms

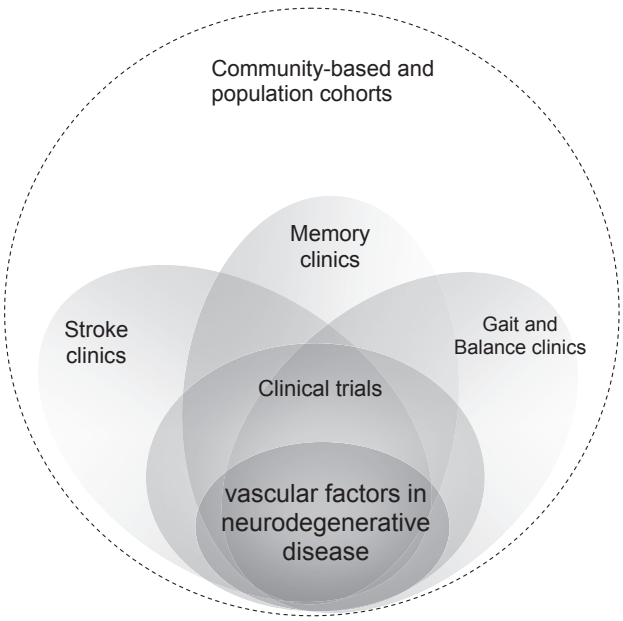

Fig. 1. Approaches to tackling vascular factors in neurodegenerative disease. The challenge is to integrate the different clinical presentations when attempting to recognize more completely the interactions between vascular disease and neurodegeneration and thence improve prevention and treatment.