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Featured Article

Concomitant vascular and neurodegenerative pathologies double the risk of dementia

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Abstract

Introduction: The relative contributions of vascular and degenerative pathology to dementia are unknown. We aim to quantify the proportion of dementia explained by potentially preventable vascular lesions.

Methods: We systematically searched for population-based cohorts before February 2017 reporting clinicopathological data for individuals with and without dementia. We calculated the summary proportion and absolute risk of dementia comparing subjects with and without the pathology.

Results: We identified 10 studies comprising 2856 subjects. Vascular-type pathology and mixed pathology are respectively two and three times more likely in demented patients. The summary proportion of dementia is 77%–86% in subjects with mixed degenerative and vascular pathology and 45% in subjects with pure Alzheimer-type pathology.

Discussion: Patients with mixed pathologies have nearly twice the incremental risk of dementia compared with patients with only Alzheimer-type lesions. Consequently, many cases of dementia could be prevented or delayed by targeting the vascular component.

Keywords: Vascular dementia; Vascular cognitive impairment; Alzheimer's disease; Mixed dementia; Microinfarct; Macroinfarct; Tangles; Plaques; Aging; Risk; Prevention; Systematic review; Meta-analysis

1. Introduction

In 1907, Alois Alzheimer reported neuropathological findings of plaques and tangles in a middle-aged patient with psychosis [1]. Subsequent studies revealed the lesions to be frequently present in elderly patients with dementia [2]. However, neuropathological findings related to common subtypes of dementia have also been frequently reported in individuals without dementia [3–6]. The correlation between neuropathological findings and cognitive dysfunction has thus remained controversial [7]. Furthermore, the magnitude of cognitive impairment does not strictly correlate with the burden of degenerative neuropathology. This discrepancy between pathological findings and cognitive performance is more common in patients over 80 years of age, who are more likely to have multiple brain pathologies [8,9], than in younger subjects [7].

All the authors have no conflicts of interest.

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Vascular lesions are frequently present in patients with dementia, alone or in combination with other brain pathologies [4,10–12]. There has been growing interest in identifying the role of vascular lesions in elderly patients with dementia because many vascular risk factors are controllable or preventable at the brain-at-risk stage [13]. However, there is no consensus on the contribution of vascular lesions, on their own and in combination with other neuropathologies, and on the risk and burden of dementia.

We performed a systematic review and meta-analysis of population-based studies reporting neuropathological findings in subjects with and without dementia. We aimed to quantify the increased risk of dementia associated with vascular lesions compared with Alzheimer-type neurodegenerative lesions.

2. Methods

2.1. Literature search

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [14]. A comprehensive search was performed in Medline via Ovid (1946 to February 2017), Embase (1947 to February 2017), Scopus (1966 to February 2017), and Web of Science (1900 to February 2017) for prospective population-based observational studies with various keywords and their synonyms (Supplementary Table A), containing major categories of relevant terms, including suitable population (adults and the elderly with no age limit), condition (dementia and cognitive decline), neuropathologies related to dementia (vascular-type and Alzheimer-type pathologies, that is, microinfarct, macroinfarct, lacunar disease, small-vessel disease, tangles, and plaques), and type of studies (population-based and prospective studies). No language, date, and publication restrictions were applied. After deleting duplicates (Supplementary Table B), references were imported into the Covidence platform for title and abstract review. References of included articles and reviews were crosschecked to identify additional studies.

2.2. Selection criteria

Two authors (M.R.A. and A.A.) independently screened citations and selected potentially relevant papers per their titles and abstracts. During the full-text review, studies fulfilling all the following criteria were included for final analyses: full-length reports published in peer-reviewed journals, subjects underwent standard neuropsychological examination on a regular basis, and subjects underwent standard neuropathological assessments after death. Studies with any of the following characteristics were excluded: not population-based cohorts, without brain pathology data, duplicated reports or nonoriginal research papers, and lacking adequate data for extraction. Conflicts were resolved between the two authors through discussion, and in case of a disagreement, a third person, V.H., helped with the final decision.

Studies were classified into three major groups: papers with a final clinicopathological diagnosis of dementia, papers with detailed pathologies, and papers with multivariate analysis. Four reports of three population-based cohorts, despite having pathology data, were not used in our analysis. The 2013 report of the Oregon Brain Aging Study [15] was excluded because they combined the data of cognitively impaired and demented subjects. Furthermore, its 2000 report with 19 subjects [16] was excluded because detailed pathology data were not available. The 2001 report of The Memory and Aging Project at Washington University [17] was not included in the analysis of vascular lesions, as the type and topography of lesions were not indicated. Likewise, the 1996 report of the Baltimore Longitudinal Study of Aging [18] presenting 22 initial autopsies was excluded, due to the insufficient detailed information of all brain lesions.

2.3. Data extraction

A flow chart of the screening and identification of studies is shown in Fig. 1. M.R.A. and A.A. independently abstracted data, including study characteristics (study population, methods used to test cognitive status and dementia, methods used to evaluate brain pathology, follow-up intervals, and time to death from the last follow-up evaluation) and patient characteristics (mean age, sex, education, cognitive status, brain weight, and neuropathological findings at autopsy, including methods of investigation). Dementia status was based on the last follow-up evaluation before death. Studies were evaluated for sources of bias. "Nondemented" included patients who were cognitively normal and those with mild cognitive impairment.

The detailed pathologies of interest were tangles and plaques (related to Alzheimer's disease), microinfarcts, macroinfarcts, lacunar disease, and small-vessel disease. We substratified by topography, for example, neocortical, subcortical, hippocampal, entorhinal, and by amounts of microinfarcts. Based only on neuropathological findings in each study, we classified patients as having primary vascular-type pathology, primary Alzheimer-type pathology, mixed vascular- and Alzheimer-type pathology, or normal brain (i.e., no/negligible pathology). Vascular lesions include atherosclerosis of cerebral vessels, cerebral small vessel disease (i.e., small vessel arteriosclerosis, lipohyalinosis, and arteriolosclerosis), and brain infarcts comprising infarcts of >1 cm in diameter (macroinfarcts), 0.5–1.0 cm (lacunar infarcts), and <0.5 cm (microinfarcts) [19,20]. White matter changes (i.e., white matter pallor in brain pathology, which is presented as white matter hyperintensity on magnetic resonance imaging) and cerebrovascular amyloid angiopathy were not in the scope of the present study. Full descriptions