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Featured Article

Microinfarcts are common and strongly related to dementia in the oldest-old: The 90+ study

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Abstract

Introduction: We estimated the prevalence of microinfarcts and their association with dementia in a cohort of oldest-old participants.

Methods: Participants were from The 90+ Study, a population-based study of people 90 years and older. Dementia diagnoses were assigned postmortem during a consensus conference. Microinfarcts were evaluated in six brain regions.

Results: At death, the 213 participants were on average 97 years old, 69% were women, and 52% had dementia. Of the participants, 51% had microinfarcts and 17% had 3+ microinfarcts. The odds ratio (OR) for dementia was similar for 3+ microinfarcts (OR = 4.75, $P < .01$) and tangle stage V–VI (OR = 4.70, $P < .001$). Only microinfarcts in cortical regions (other than occipital) were associated to dementia.

Discussion: In this oldest-old cohort, microinfarcts are common and contribute independently and similarly in magnitude to dementia as tangles. As risk factors for microinfarcts and other dementing pathologies are likely to differ, identifying these factors is crucial to developing prevention strategies for dementia in the oldest-old.

Keywords: Oldest-old; Cohort studies; Epidemiology; Dementia; Alzheimer's disease; Neuropathology; Microinfarctions; Brain infarctions

1. Introduction

Large vessel vascular pathologies have long been considered an important contributor to dementia [1]. Microvascular pathologies, such as microinfarcts, are typically given less attention but some have found microinfarcts to be a contributor to dementia as important as Alzheimer disease (AD) pathology [2,3]. Studies suggest that the prevalence of microinfarcts increases with age [4]. Given that rates of dementia also increase with age, it would be natural to hypothesize that microinfarcts may be related to dementia at very advanced ages. The average age of death of participants in most studies to date that evaluate microinfarcts is <90 years, but the one study with an average of 90.7 years reported that microinfarcts were very prevalent, detected in almost half of the participants (48%) [5] and was strongly related to dementia. With the fast-growing numbers of oldest-old people (those 90 and older) in the United States and many other countries and with their very high rates of dementia [6], identifying factors related to the development of dementia in the oldest-old is crucial. Our work has two main objectives: (1) to estimate the prevalence of microinfarcts and (2) to study the association between the presence of microinfarcts and the likelihood of dementia after adjusting for the presence of other dementing pathologies in a cohort of oldest-old participants.

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2. Methods

2.1. Participants

Participants were members of The 90+ Study, a longitudinal study of aging and dementia in people aged 90 years and older. Participants in The 90+ Study are survivors from the Leisure World Cohort Study (LWCS), an epidemiologic investigation in a Southern California retirement community. In the early 1980s, all residents of the community were mailed a health survey and those who returned it constitute the LWC. All LWCS participants, with or without dementia, who were alive and ≥90 years in January 1, 2003 were invited to participate in The 90+ Study. A similar invitation was extended to participants who turned 90 years on January 1, 2008 and every year thereafter. All 90+ Study participants who agreed to in-person examination (N = 978) were invited to be part of the autopsy program [7]. A small number of people who were not part of the original LWCS but lived in the same region (N = 25) were also recruited. As of December 31, 2013, 354 participants had enrolled in the autopsy program, representing 36% of those invited to the program. Of the 354 participants enrolled, 239 died and of those, 219 came to autopsy (92% autopsy rate). All participants or their designated informants provided consent to participate in the study. All procedures were reviewed and approved by the University of California, Irvine (UCI) Institutional Review Board.

2.2. Pathologic evaluations

All procedures for procuring and preparing tissues were performed by the UCI Alzheimer's Disease Center Pathology Core in harmony with uniform data sets and forms of the National Alzheimer Coordinating Center. If the examiner performing the neurologic evaluation found clinical signs of stroke, the affected hemisphere was pre-specified for pathologic evaluation. If there were no clinical signs, the left hemisphere was selected for evaluation. Brain cutting was performed after approximately 2 weeks of fixation and regions of interest (middle frontal, superior temporal, inferior parietal, occipital, entorhinal, and cingulate gyri, as well as basal ganglia, thalamus, hippocampus, amygdala, midbrain, pons, medulla, and cerebellum) were paraffin-embedded and sectioned. Two board-certified neuropathologists performed all pathologic evaluations blinded to clinical diagnosis. Joshua Sonnen performed all evaluations for microinfarcts with the same methodology, he applied in other population-based cohorts [2,3] and Ronald Kim performed evaluations for other pathologies.

The presence of microinfarcts was assessed as suggested by the NIA-AA guidelines [8] using one Hematoxylin & Eosin–stained brain tissue section for each of six predefined regions: middle frontal, inferior parietal, superior temporal, occipital, basal ganglia, and thalamus. Microinfarcts were defined as foci of pallor, loss of vulnerable cells, gliosis, and macrophage presence [2]. These measures pioneered in the Honolulu Asia Aging Study (HAAS) [2] have been validated in other population-based and community-based autopsy studies [9]. The adjacent white matter in the sections of the middle frontal, inferior parietal, superior temporal, occipital, and basal ganglia was available. Thus, microinfarcts were evaluated in both gray and white matter for these regions, although white was not as heavily sampled as gray matter. Macroinfarcts were defined as ischemic and hemorrhagic infarcts identified grossly at the time of dissection. These infarcts were evaluated for size, location, and number. Infarcts coded by the pathologist as either large infarcts or lacunes are included in this category. Acute and subacute macroinfarcts proximal to death were excluded. Neurofibrillary tangle pathology was graded with Braak & Braak staging [10] and neuritic plaque pathology categorized according to CERAD score [11]. Subcortical arteriolosclerotic leukoencephalopathy was assessed within periventricular white matter immediately adjoining the rostral cingulate gyrus and caudal cingulate gyrus and was defined by lipohyalinosis and/or arteriolar sclerosis, widening of perivascular spaces, white matter gliosis, and pallor of myelin staining [12]. Cerebral amyloid angiopathy (CAA) was assessed with β-amyloid immunostaining of cerebral blood vessels and classified as absent, mild, moderate, or severe. Details about the pathologic evaluations have been published previously [13].

2.3. Evaluations and dementia determination

Participants were examined every 6 months, and evaluations included a neurological examination, physical examination, neuropsychological battery, review of medical history, and interviews with knowledgeable informants. After a participant's death, we performed additional interviews with informants to inquire about cognition and function since last evaluation. We assigned dementia diagnoses (DSM-IV) [14] during a consensus conference using all available clinical information including longitudinal evaluations, brain imaging when clinically available, informant questionnaires, and medical records. One of the authors (C.K.), a geriatric neurologist, led the consensus conferences, with conferees blinded to pathologic evaluations. As we wanted to examine the association between dementia (a clinical diagnosis) and pathologic findings, the two assessments were performed independently of each other.

2.4. Additional variables

Demographic and medical history information were reported by participants or their surrogates if cognitively impaired. Relevant medical histories include cardiovascular and cerebrovascular histories, which consist of stroke, transient ischemic attack (TIA), diabetes, and heart disease. We considered history of heart disease present if any of the following were reported: coronary artery disease, myocardial infarction, atrial fibrillation or other arrhythmias, heart