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Perspective

White matter hyperintensity burden in elderly cohort studies: The Sunnybrook Dementia Study, Alzheimer's Disease Neuroimaging Initiative, and Three-City Study

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Abstract Given the recent acknowledgement of the complex mixed pathologies that contribute to the clinical expression of dementia, various cohort studies have aimed to examine Alzheimer's disease and cerebrovascular disease as comorbid pathologies, with neuroimaging playing a central role in these studies. Using white matter hyperintensities (WMH) as a biomarker of cerebrovascular disease, we compared WMH burden between the Sunnybrook Dementia Study, the Alzheimer's Disease Neuroimaging Initiative (ADNI-1), the Three-City Study, and various other studies around the world. Based on our findings, it was evident that ADNI-1 had minimal WMH burden relative to other large studies that examine aging and dementia. This low WMH burden in ADNI-1 may be considered as both an advantage, representing a relatively "pure" sample with little confounding vasculopathy, and a disadvantage, as it limits generalizability to "real-world" patient populations with mixed pathologies and to nondemented groups with baseline vascular disease. We explore possible reasons for this distinction, including management of vascular risk factors, gaps in diagnostic criteria, and future directions for clinical research.

Keywords: Alzheimer's disease; Cerebrovascular disease; Aging; White matter hyperintensities; Dementia; Elderly cohort; Population studies

1. Introduction

Dementia affects approximately 44 million people worldwide according to current estimates, a number that is predicted to more than triple to 135 million by 2050 [1]. As Alzheimer's disease (AD) and vascular cognitive disorders are the top two leading primary causes of dementia [2], recent studies examining the contribution of modifiable risk factors for dementia have acknowledged cerebrovascular pathology as a primary concern [3–6], with neuroimaging playing a central role in many of these studies [7]. As most dementia cases are mixed pathologies with some vascular component [8], many present studies have increased their

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focus toward understanding the role of vasculopathy, vascular brain injury, and the management of vascular risk factors [9,10], in the context of AD pathophysiology [11–13].

As recently defined by an international consensus process, white matter hyperintensities (WMH) of presumed vascular origin, visible on structural magnetic resonance imaging (MRI), are commonly used markers of cerebrovascular disease [7]. Clinicopathologic correlations suggest WMH to be indicative of cerebral small vessel disease [7,14], potentially originating from ischemic tissue damage caused by arteriosclerosis [15,16], vasogenic edema induced by periventricular venous collagenosis [17,18], and cerebral amyloid angiopathy [19–21]. These imaging-based biomarkers of cerebral small vessel disease have been associated with increased age, vascular risk factors, mild cognitive impairment (MCI), and AD [22–24].

In this article, we chose to examine imaging markers of small vessel disease within three large neuroimaging studies: the Sunnybrook Dementia Study (SDS: Canada), the Alzheimer's Disease Neuroimaging Initiative Phase 1 (ADNI-1: mainly US), and the Three-City Study (3C: France). We examined these studies because (1) they were relatively contemporary, having been conducted around the same time, (2) the populations were sampled primarily from different countries, (3) the imaging acquisition protocols (at 1.5 tesla) were comparable, (4) WMH volumes were quantified using proton density and T2-weighted (T2) MRI sequences (i.e., non-FLAIR based), and (5) study samples were elderly, aged 50–90 years.

2. The Sunnybrook Dementia Study, Alzheimer's Disease Neuroimaging Initiative, and Three-City Study

The SDS [25] is a prospective cohort study (1994–2014) conducted at the Sunnybrook Heath Sciences Centre–University of Toronto, in Toronto, Canada (ClinicalTrials.gov NCT01800214). One goal of the SDS was to examine a real-world cohort of dementia patients and normal elderly (50–90 years old) and the potential impact of comorbid cerebral small vessel disease manifested primarily as covert lacunes and white matter lesions.

The ADNI-1 [26] is a large multisite longitudinal brain imaging study based in the United States (53 sites) and Canada (5 sites). The first phase, ADNI-1 (2004–2010), examined patients with AD, MCI, and normal elderly controls (NC), aged 55–90 years. The study's primary objectives included the identification of biomarkers to identify AD at the earliest stage so that intervention, prevention, and treatment of dementia could be more effective (See Supplementary Material 1 for additional details).

The 3C [27] is a multicenter, longitudinal population–based cohort study (1999–2012) conducted in three cities in France: Bordeaux, Dijon, and Montpellier. The goal of the 3C study was to examine the associations of vascular risk with dementia and cognitive impairment. Participants were randomly sampled from electoral rolls and aside from age (65–80 years), there were no exclusion criteria. The subsample examined in the present study included 1701 nondemented elderly with a mean mini-mental state examination (MMSE) of 28, suggesting a relatively normal sample. Unfortunately, stratification by cognitive status was not possible because diagnostic criteria for MCI were not implemented on entry into the 3C study.

3. WMH findings in dementia and the elderly: ADNI-1, SDS, and 3C

To compare WMH volumes between SDS and ADNI-1, we plotted head-size corrected WMH volumes by age to visually examine the distributions across the diagnoses (Dx; Fig. 1). To account for differences in disease severity for the AD groups, we only included patients with MMSE scores $\geq$20 (based on ADNI-1 inclusion criteria). On visual inspection of the graphs displayed in Fig. 1, it was evident that there were very obvious differences in the distribution of WMH in these two cohort studies. Additionally, similar differences were demonstrated for all Dx groups within each sample, with the SDS samples exhibiting greater age-related WMH volumes compared with the ADNI-1 samples.

As further demonstrated in Table 1, these differences can also be seen with group average and variability statistics, whereby the SDS sample displayed more variability and higher average WMH volumes across all Dx groups when compared with ADNI-1 (all significant, $P < .001$, Table 1). Additionally, population-based data recently reported by the 3C group [28] were also included for relative comparison (Table 1). Based on these results, the vascular burden, indicated by WMH volumes, was much greater in the SDS and 3C samples than in the ADNI-1 sample.

Additionally, because WMH volumes typically exhibit a nonnormal, often highly skewed distribution, the reporting of standard statistical measures for central tendency and spread may not be appropriate for proper visualization of the data. Given this phenomenon, we have also provided a breakdown of the proportional distributions by range of WMH in the SDS and ADNI-1 samples. As shown in Fig. 2, compared with 22% in the SDS sample, 83% of the ADNI-1 sample presented with less than 1 cc of WMH (dark green) across all Dx groups. Conversely, although over a third of the SDS sample had over 5 cc of WMH (warm colors: yellow, orange, and red), less than 3% of the ADNI-1 sample had significant volumes of WMH. Although this could be due to a difference in the proportional representation of AD and MCI patients between the two studies, similar patterns are observed in the NC samples (albeit to a lesser degree). Interestingly, only the MCI and NC groups in ADNI-1 had any subjects with WMHs exceeding the 20-cc mark (red), a proportional representation made up of three individuals (MCI: n = 2, NC: n = 1) who would be considered as statistical outliers for both groups. Overall, in contrast to the positively skewed distribution of WMH