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Cerebral microbleeds in a multiethnic elderly community: Demographic and clinical correlates

Anne F. Wiegman [a], Irene B. Meier [a], Nicole Schupf [a,b,c], Jennifer J. Manly [a,b,d], Vanessa A. Guzman [a], Atul Narkhede [a], Yaakov Stern [a,b,d], Sergi Martinez-Ramirez [e], Anand Viswanathan [e], José A. Luchsinger [c,f], Steven M. Greenberg [e], Richard Mayeux [a,b,c,d], Adam M. Brickman [a,b,d,*]

[a] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[b] G.H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[c] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA
[d] Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[e] Massachusetts General Hospital, Stroke Research Center, Boston, MA, USA
[f] Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, USA

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ABSTRACT

Background: Microbleeds, small perivascular collections of hemosiderin manifested radiologically as hypointensities on gradient-echo magnetic resonance imaging (MRI), are important markers of small vessel pathology. Despite their clinical relevance, little is known about their prevalence and demographic correlates, particularly among ethnically diverse older adults. We examined demographic and clinical correlates of regional microbleeds in a multi-ethnic cohort and examined categorization schemes of microbleed distribution and severity.
Methods: Between 2005 and 2007, 769 individuals participated in a MRI study as part of the Washington Heights/Inwood Columbia Aging Project. Approximately four years later, 243 out of 339 participants (mean age = 84.50) who returned for a repeat MRI had gradient-echo scans for microbleed assessment and comprised the sample. We examined the association of deep and lobar microbleeds with age, sex, education, vascular factors, cognitive status and markers of small vessel disease.
Results: Sixty-seven of the 243 (27%) participants had at least one microbleed. Individuals with microbleeds were more likely to have a history of stroke than individuals without. When categorized as having either no microbleeds, microbleeds in deep regions only, in lobar regions only, and both deep and lobar microbleeds, hypertension, proportion of strokes, and white matter hyperintensity volume (WMH) increased monotonically across the four groups. The number of lobar microbleeds correlated with WMH volume and diastolic blood pressure.
Conclusions: Microbleeds in deep and lobar locations are associated with worse outcomes than microbleeds in either location alone, although the presence of lobar microbleeds appears to be more clinically relevant.

1. Introduction

Cerebral microbleeds are perivascular collections of hemosiderin that manifest radiologically as focal signal loss on T2*-weighted gradient-echo magnetic resonance imaging (MRI). Together with white matter hyperintensities (WMH) and lacunar infarcts, microbleeds have recently emerged as an important third MRI marker of small vessel pathology. They are frequently seen among healthy older adults and their prevalence increases with age [1–3]. When distributed in deep and infratentorial regions, such as the basal ganglia, thalamus and brainstem, microbleeds typically are the result of hypertensive vasculopathy [3]. When they appear in cortical and subcortical regions of the cerebral lobes (i.e., "lobar" distribution), microbleeds typically reflect hemorrhagic lesions attributable to cerebral amyloid angiopathy (CAA), which refers to the deposition of beta-amyloid in the media and adventitia of small cerebral arterioles [3–5]. (See Fig. 1.)

Microbleeds are relevant to cognitive aging in three ways. First, community-based studies and studies with patients meeting clinical criteria for CAA [6] have suggested that higher numbers of microbleeds, as a proxy measure of the severity of CAA pathology, are related to poorer cognition [7–9]. Second, consistent findings have implicated markers of cerebrovascular disease in the clinical presentation and pathogenesis of Alzheimer's disease (AD) [10–13]. That the vast majority of patients with AD have evidence of CAA at autopsy [14] provides

* Corresponding author at: Taub Institute for Research on Alzheimer's Disease and the Aging Brain, PS Box 16, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA. Tel.: +1 212 342 1348; fax: +1 212 342 1838.
E-mail address: amb2139@columbia.edu (A.M. Brickman).

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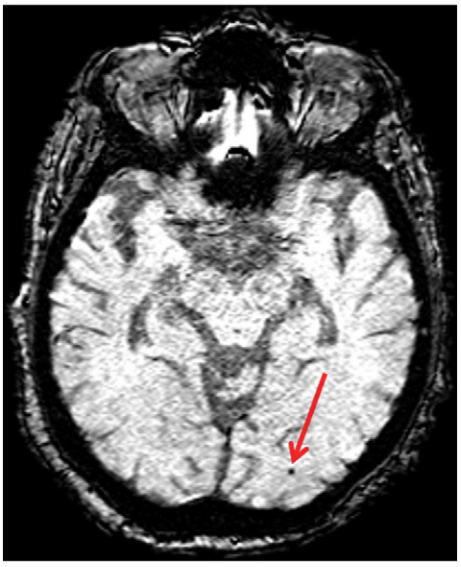

Fig. 1. Example of a microbleed in posterior distribution (red arrow).

evidence of a mechanistic link between cerebrovascular disease and the pathogenesis of AD. Finally, with the implementation of novel anti-amyloid treatments for AD comes the clinical risk of developing microbleeds, or the so-called "amyloid-related imaging abnormalities" (ARIA-H) [15,16]. Despite the clinical importance of microbleeds, little is known about their prevalence and clinical and demographic correlates, particularly among racially and ethnically diverse older adults who increasingly comprise the aging population.

The purpose of this study was to examine the demographic and clinical correlates of lobar and deep microbleeds in a multi-ethnic, community-based cohort of older adults residing in northern Manhattan. Based on the extant literature [2,3,17–19] we examined age, sex, education, vascular risk factors (hypertension, blood pressure, diabetes history, smoking history), and cognitive status (dementia, mild cognitive impairment). We were also interested in determining whether microbleeds were related to white matter hyperintensities and history of clinical stroke. Furthermore, there is currently no consensus on how to categorize best the severity of microbleeds. It is unclear, for example, whether simply having a microbleed or the regional (deep or lobar) distribution or number of microbleeds is clinically relevant. So, a second goal was to examine various categorization schemes of the distribution and severity of microbleeds as they relate to these demographic and clinical variables.

2. Methods

2.1. Participants

Participants were drawn from the Washington Heights/Inwood Columbia Aging Project (WHICAP), an ongoing prospective community-based longitudinal study of aging and dementia in northern Manhattan, New York, in residents aged 65 and older that began in 1992. The recruitment procedures and sampling strategies have been described in detail in earlier work [20]. Participants received a full medical, neurological, and neuropsychological examination at each of the follow-up visits, approximately every 18 to 24 months. Beginning in 2005, participants who did not meet criteria for dementia at their previous follow-up were invited to participate in a high-resolution MRI study, as previously described [21]. As a result, 769 participants underwent high resolution structural MRI ("baseline MRI"). The individuals who were eligible for MRI but refused participation, were 1 year older, more likely to be women, and more likely to be African American compared with the recipients of a MRI [21]. Among the 769 individuals with MRI scanning, 52 met diagnostic criteria for dementia at the clinical visit that was closest to the MRI scan.

Beginning in 2009 we invited active participants who had baseline MRI scans and were not demented at that time to return for a repeat MRI scan. We completed repeat MRI scans on 339 participants approximately 5 years after their baseline scans. Of the 339 participants, we acquired gradient echo (GRE) scans for microbleed assessment on 243 of them. Compared with the 526 participants who did not have GRE scans, those with GRE scans were similar in age ($t(766) = 1.782$, $p = 0.075$), sex distribution ($\chi^2(1) = 0.998$, $p = 0.318$), and race/ethnicity ($\chi^2(3) = 1.836$, $p = 0.607$) at baseline. They were also similar in terms of the presence of the APOE ε4 allele ($\chi^2(1) = 0.007$, $p = 0.932$), history of heart disease ($\chi^2(1) = 0.214$, $p = 0.643$), history of diabetes ($\chi^2(1) = 1.171$, $p = 0.279$), and smoking history ($\chi^2(1) = 0.684$, $p = 0.710$). Participants without GRE scans were more likely to have a clinical history of stroke (17% vs. 9%; $\chi^2(1) = 5.619$, $p = 0.018$).

2.2. MRI protocol

An optimized, high-resolution three-dimensional T2*-weighted GRE image (TR = 45 ms, TE = 31 ms, flip angle = 13, slice thickness = 2 mm) was acquired for microbleed visualization and quantification on a Philips Intera 1.5T MRI scanner (Best, the Netherlands). Fluid attenuated inversion recovery (FLAIR) T2-weighted MRI scans (TR = 11,000 ms, TE = 144 ms, 3 mm slice thickness) were acquired for white matter hyperintensities (WMH) quantification. T1-weighted images acquired for additional processing (TR = 20 ms, TE = 2.1 ms, 1.3-mm slice thickness).

Microbleeds were rated by visual inspection following criteria put forth by Greenberg and colleagues [5]. These criteria include the following parameters: a dark (black) lesion on T2*-weighted MRI, which is round or ovoid shaped, surrounded at least half way by parenchyma, and accompanied by a "blooming" effect. The microbleed is devoid of signal hyperintensity on accompanying T1- or T2-weighted sequences and is distinct from other mimics, such as iron or calcium deposits, bone, or vessel flow voids. Microbleeds were classified by location, which included "lobar" in frontal, temporal, parietal, and occipital lobes and "deep," which included basal ganglia, thalamus, and infratentorial regions. The number of microbleeds and location were coded for each subject. A single operator (IBM) performed all the microbleed reads after achieving excellent inter-rater reliability (ICC > 0.93) on a training data set that had been evaluated by an expert (SMR).

Because there is no consensus in the extant literature about the best classification scheme for microbleeds among community participants, we considered the distribution in three distinct ways. First, we compared individuals with at least one microbleeds to those with no microbleeds. Next, we categorized subjects into four mutually exclusive groups, which included no microbleeds, 1 or more deep microbleeds ("deep only"), 1 or more lobar microbleeds ("lobar only"), and 1 or more deep microbleed and 1 or more lobar microbleed ("deep and lobar"). Finally, because of the hypothesized link between lobar microbleeds and beta amyloid, we considered lobar microbleeds as a continuous variable to examine "dose response" individual differences.

Total WMH volume was determined following procedures previously described in detail [22,23]. Briefly, FLAIR images were skull-stripped and a threshold and seed-growing algorithm was applied to identify voxels that fell within an a priori-determined distribution of hyperintense signal. Labeled voxels were summed and multiplied by voxel dimensions to yield total WMH volume. Because the distribution of WMH volume is positively skewed, we log transformed the data.