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Research article

Cerebral autoregulation, beta amyloid, and white matter hyperintensities are interrelated

Adam M. Brickman[a,b,c,*], Vanessa A. Guzman[a], Miguel Gonzalez-Castellon[c], Qolamreza Razlighi[a,c], Yian Gu[a,c], Atul Narkhede[a], Sarah Janicki[a,b,c], Masanori Ichise[d], Yaakov Stern[a,b,c], Jennifer J. Manly[a,b,c], Nicole Schupf[a,b,c,e], Randolph S. Marshall[c]

[a] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, USA
[b] G.H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, USA
[c] Department of Neurology, College of Physicians and Surgeons, Columbia University, USA
[d] Department of Radiology, College of Physicians and Surgeons, Columbia University, USA
[e] Department of Epidemiology, Mailman School of Public Health, Columbia University, USA

HIGHLIGHTS

- Vascular risk factors are associated with risk for Alzheimer's disease.
- We examined cerebral autoregulation, cerebrovascular disease, and amyloid in older adults.
- The three factors correlated with each other.
- Autoregulation, cerebrovascular disease, and amyloid pathology are interrelated.

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ABSTRACT

Emerging studies link vascular risk factors and cerebrovascular health to the prevalence and rates of progression in Alzheimer's disease (AD). The brain's ability to maintain constant blood flow across a range of cerebral perfusion pressures, or autoregulation, may both promote and result from small vessel cerebrovascular disease and AD-related amyloid pathology. Here, we examined the relationship among cerebral autoregulation, small vessel cerebrovascular disease, and amyloid deposition in 14 non-demented older adults. Reduced cerebral autoregulation, was associated with increased amyloid deposition and increased white matter hyperintensity volume, which, in turn were positively associated with each other. For the first time in humans, we demonstrate an interrelationship among AD pathology, small vessel cerebrovascular disease, and cerebral autoregulation. Vascular factors and AD pathology are not independent but rather appear to interact.

1. Introduction

There is little debate that accumulation of the Aβ40 and Aβ42 cleaved products of beta amyloid precursor protein and aggregation of tau protein characterize the pathological stigmata of Alzheimer's disease (AD). However, it remains unclear which factors initiate the biological cascade of events that ultimately lead to the devastating neuropsychological syndrome that defines the disease clinically and to what extent additional etiological factors play a role in disease pathogenesis. Among the most perplexing observations from the extant literature is the relationship of vascular risk factors and markers of cerebrovascular health to the prevalence, risk, and rates of clinical progression in AD [6,18]. While clinical and epidemiological studies suggest a pathogenic link between vascular health and AD, proposed hypothetical models of disease pathogenesis, animal models, and newly implemented research diagnostic formulations have not incorporated vascular disease formally into disease conceptualization [2,22,27,38].

There are several possible models that may explain the apparent association between vascular disease and AD. First, cerebrovascular changes may reflect pathology that is independent of AD pathology,

* Corresponding author at: Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street: P&S Box 16, 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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conferring additive risk or contribution to symptom presentation [22]. Second, cerebrovascular disease may interact more directly with AD pathology by promoting beta amyloid deposition, inhibiting its clearance, and thus having a synergistic effect on clinical outcomes [43]. Third, the relationship between cerebrovascular disease and AD pathology may be driven by a shared association with a third set of factors. In order to begin to determine the extent to which these possibilities are operative, a better understanding of the specific relationship between cerebral hemodynamics and amyloid pathology is needed.

We previously demonstrated that the white matter hyperintensities (WMH) volume, a magnetic resonance imaging (MRI) marker of small vessel cerebrovascular disease, is associated with increased risk and progression of AD [7,8,10,13,26]. Among individuals with evidence of cerebral fibrillar amyloidosis, we showed that those with higher amounts of WMH were more likely to meet diagnostic criteria for clinical AD [35], raising the possibility of an interaction or bidirectional relationship between small vessel arterial disease [41] and AD pathology.

If this bidirectional relationship does indeed exist, it may be mediated by individual differences in hemodynamics [17]. The brain is one of the few organs that regulates its own blood flow, and the only one in which "autoregulation" is crucial to its function. Via interacting myogenic, neurogenic, and metabolic mechanisms, brain blood flow is maintained at a constant level across a wide range of cerebral perfusion pressures [32,40] in a process referred to a cerebral autoregulation. Autoregulatory dysfunction is associated with small vessel cerebrovascular disease [24], and, directly or indirectly may promote deposition and prevent clearance of amyloid pathology [3,17,21,23]. Amyloid pathology itself can disrupt autoregulatory function via impairment of vasodilatory response [14,17,40]. In the current study we examined the relationship among markers of small vessel cerebrovascular disease (i.e., WMH), fibrillar amyloid deposition, and autoregulatory dysfunction. We hypothesized that these three factors would be interrelated.

2. Material and methods

Fourteen non-demented participants from the Washington Heights Inwood Columbia Aging Program (WHICAP), an ongoing study of cognitive aging, received transcranial Doppler ultrasonography (TCD) to evaluate dynamic cerebral autoregulation (DCA). One subject met criteria for mild cognitive impairment. We computed a mean cognitive summary score by averaging summary scores for memory, language, executive, and visuospatial abilities (see [28]) and participants scored well within normal limits ($z = 0.53$, SD = 0.54). Subjects were invited to participate in this substudy if they had received a PET scan to evaluate fibrillar amyloid deposition and MRI scan as part of the parent project. Vascular disease history was determined as previously described [11]. Dichotomous variables, coded as 0 (not present) or 1 (present) based on clinical history or current treatment for diabetes, hypertension, and heart disease were summed to create a single vascular risk summary score ranging from 0 to 3.

The study received ethics review and approval from the Institutional Review Board and written consent was obtained from all participants.

2.1. Magnetic resonance imaging

Participants were scanned on a 1.5 T Philips Intera scanner as previously described [11]. T1-weighted (TR = 20 ms, TE = 2.1 ms, FOV 240 cm, 256 × 160 matrix, 1.3 mm slice thickness) and T2-weighted fluid attenuated inversion recovery (FLAIR; TR = 11,000 ms, TE = 144.0 ms, inversion time = 2800, FOV 25 cm, 2 nex, 256 × 192 matrix with 3 mm slice thickness) images were acquired in the axial orientation. White matter hyperintensity volume was derived using procedures described previously [9,10,12]. Briefly, a Gaussian curve was fit to map the voxel intensity values. Voxels falling above 3.0SD of the image mean were labeled as WMH. Labeled voxel values were multiplied by voxel dimensions and summed to yield total volumes in cm^3. Volumes were log transformed.

2.2. Amyloid positron emission tomography (PET) imaging

Presence and quantity of fibrillar amyloid deposition was determined with ^{18}F-florbetaben PET imaging. Each participant received intravenous catheterization followed by a single bolus injection of 10 mCi ^{18}F-florbetaben. An MCT PET/CT scanner (Siemens) acquired PET scans over 20 min (4 × 5 min frames) in dynamic, 3-dimensional imaging mode beginning 50 min after injection of the tracer. At the time of PET scanning, an accompanying structural CT scan (0.58 × 0.58 × 3 mm, field of view = 29.6 × 29.6 cm^2, number of slice = 75) was acquired.

Amyloid deposition was evaluated with both visual (clinical) rating and quantitatively. Visual ratings followed a method similar to what was reported by Barthel et al. [5]. Each PET scan was reviewed independently by two experts (SJ and MI), blind to clinical and demographic information. Florbetaben binding was evaluated in frontal cortex, temporal cortex, parietal cortex, posterior cingulate, and occipital cortex. Each region received a positive or negative rating depending on whether the uptake was perceived to be greater than the adjacent white matter. An overall clinical, dichotomous rating of "positive" was assigned if any of the regions was considered to be positive. Discordant cases were reviewed by the two raters together and a final consensus rating was assigned together.

For quantitative PET analysis, T1-weighted structural MRI scans were analyzed with Freesurfer (http://surfer.nmr.mgh.harvard.edu/) to derive anatomical regions-of-interest (ROIs). Four ROIs from each cerebral hemisphere, including frontal cortex, temporal cortex, parietal cortex, and cingulate gyrus, were extracted from each subject's T1-weighted MRI scan. The four dynamic PET frames were aligned to the first frame and a single PET image was derived by averaging the frames. The single scan was registered to the CT scan to derive a transformation matrix. Each individual's T1-weighted MRI scan was also registered to the participant's CT image with normalized mutual information and tri-linear interpolation to derive a second transformation matrix.

A combination of the two transformation matrices was used to transfer the regional freesurfer ROI masks and the cerebellar gray matter to the single PET image space with nearest neighbor interpolation. These four regional masks were used to extract the regional PET data. The standardized uptake value (SUV), defined as the decay-corrected brain radioactivity concentration normalized for injected dose and body weight, was calculated in each region. The SUV was then normalized to the mean cerebellar grey matter to derive a standardized uptake value ratio (SUVR). The mean SUVR in the four ROIs was derived as a quantitative measure of amyloid uptake.

2.3. Dynamic cerebral autoregulation

Transcranial Doppler ultrasongraphy combined with continuous blood pressure monitoring were used to evaluate DCA, as has been described previously [31,33]. Briefly, cerebral blood flow velocities (CBFV) were assessed using TCD (DWL-Multidop-X, Sipplingen, Germany). The left and right proximal middle cerebral arteries (MCA) were insonated through the temporal window with a 2 MHz probe attached to a standard head frame, insonation