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Cerebral autoregulation, beta amyloid, and white matter hyperintensities 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.

Keywords

Cerebral autoregulation; White matter hyperintensities; Amyloid; Alzheimer's disease

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

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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, 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 sub-study 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 = 2.1ms, 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 depth = 45–56 mm. Blood pressure was recorded simultaneously and continuously using servo-controlled finger plethysmography (Finapres: Finometer Pro Amsterdam, Netherlands). The appropriate finger cuff (small, medium or large) was placed on the middle phalanx of the left or right middle finger. After establishing a stable recording and calibration, measurements were recorded for 10 min. All analog signals were digitized and stored for editing and offline analysis. Data sampling frequency was 100 Hz.

The relationship between changes in arterial pressure and CBFV was assessed with transfer function analysis, which quantifies the spatial relation between slow oscillatory fluctuations in arterial blood pressure (ABP) and oscillations in CBFV in the same frequency domain [19,37].

Arterial blood pressure and CBFV from the left and right middle cerebral arteries were normalized and fast Fourier transformed to calculate the auto-spectra and the cross spectrum of the two signals (ABP and CBFV). The phase $\Phi(f)$ of the system was calculated for the two streaming signals. Coherence significance criterion (γ_{min}), above which coherence differs significantly from 0, was derived from the degrees of freedom ν of the spectral estimate at a significance level α of 0.05 [20]. Phase shift was calculated by averaging the values of all valid bins in the low-frequency range (0.06–0.12 Hz; each bin is a frequency value at 0.01 Hz increments) where coherence was >0.53.

The resulting phase shift describes the extent to which oscillations in CBFV lead those in ABP and can be interpreted as active early counter-regulation. Less phase shift reflects increased latency in cerebral vasomotion and thus poorer autoregulation [1,25].

2.4. Statistical analysis

Bivariate correlations were used to explore the relationship among left and right hemisphere MCA phase shift, amyloid burden, and WMH volume. For amyloid burden, we considered the continuous measure mean amyloid uptake values across regions-of-interest and also a dichotomous clinical rating of amyloid positivity versus negativity. We ran follow-up partial correlations, controlling for participant age.

3. Results

Complete hemodynamic, amyloid PET, and MRI data were collected on 14 older adults (mean age ± SD = 82.53 ± 3.29, 6 women). Neither age nor sex were associated with any of the variables of interest (p range = 0.421–0.910). Participants had an average of 1.79 (SD = 0.80) vascular disease risk factors. This vascular risk summary score was unrelated to any of the variables of interest in the study (p range = 0.285–0.779) and therefore not further considered in subsequent analyses. Three participants' PET scans were read to be "positive" for amyloid, though there was a range of uptake values when considered as a continuous variable (see Table 1).

Lower LMCA average phase shift was associated with amyloid positivity ($r = -0.57$, $p = 0.03$) and increased WMH volume ($r = -0.82$, $p < 0.001$). Lower LMCA average phase shift was associated with amyloid uptake with a moderate effect size ($r = -0.43$, $p = 0.13$), though the relationship did not meet statistical significance. Right MCA phase shift was non-significantly associated with amyloid burden ($r = -0.38$, $p = 0.17$) and WMH ($r = -0.27$, $p = 0.41$); hemispheric differences may have been due to an inconsistent RMCA signal in several of the patients because of a poor insonation window, leading to lower coherence in the signal. It is notable that the LMCA signal was associated with the overall WMH volume and amyloid positivity, suggesting that the LMCA phase shift was an adequate marker of the overall brain pathology. White matter hyperintensity volume was strongly associated with amyloid positivity ($r = 0.77$, $p = 0.001$) and moderately with amyloid uptake values ($r = 0.37$, $p = 0.19$), though again not significantly. Graphical presentation of the relationship of LMCA average phase shift with amyloid uptake and WMH and of WMH with amyloid uptake is presented in Fig. 1. When the correlational analyses were re-run after partialling out participant age, the findings were essentially identical.

4. Discussion

We showed that measures of autoregulatory dysfunction are related to the presence of fibrillar forms of beta amyloid and severity of WMH, which in turn are related to each other. The correlational analysis precludes our ability to infer causal relationships, but to our knowledge, these analyses are the first to provide evidence that cerebral autoregulation, small vessel cerebrovascular disease, and Alzheimer's pathology correlate in humans. Autoregulatory dysfunction is associated with small vessel disease, which in turn can

promote the deposition or inhibit the clearance of amyloid pathology [43]. Alternatively, it is possible that amyloid pathology itself leads to autoregulatory dysfunction and cerebrovascular disease via deposition of beta amyloid in blood vessels or associated endothelial dysfunction [17,23]. Finally, autoregulatory dysfunction may promote both small vessel cerebrovascular disease and amyloid pathology, producing a combined effect clinically, but the two may be related to each other epiphenomenologically (e.g., their correlation is due to their shared association with autoregulatory dysfunction). It is our hypothesis that these three possibilities are all operative, but future longitudinal work with larger samples is required to establish to what degree.

The relationship between autoregulatory dysfunction and Alzheimer's pathology has been studied extensively in animal models (see [17] for review). Transgenic mice that over-express beta amyloid showed evidence of severely impaired autoregulation, including reduced cerebral blood flow, impaired endothelium-dependent vasodilation, increased vasoconstrictor response, and compromised cerebrovascular reactivity [21,29,30]. Notably, many of these changes occur prior to the deposition of frank amyloid pathology. In humans, on the other hand, the relationship between Alzheimer's pathology and autoregulation has not been shown definitively. One study used ^{15}OPET to measure blood flow before and after mean arterial blood pressure was lowered by 15 mm Hg with intravenous nicardipine and found no concomitant change in cerebral blood flow throughout the brain, including in areas identified as having fibrillar forms of amyloid and WMH [42]. This study has been criticized however [17] because while nicardipine induces changes in blood pressure it may also increase compensatory vasodilation in the brain, thus obscuring autoregulatory dysfunction. A second criticism [17] is that ^{15}OPET lacks the temporal resolution to measure changes blood flow that would be linked to autoregulation. Some studies [39], but not all [4,15,16] did show evidence of reduced autoregulation among patients with AD, but did not evaluate Alzheimer's pathology per se. Our study is the first to be able to evaluate Alzheimer's pathology directly, induce the requisite amount of cerebral blood variability to evaluate autoregulation, and measure blood flow with high temporal resolution.

Hemodynamic dysfunction, indexed by markers of pulsatility, vasoreactivity, and dynamic cerebral autoregulation, has been associated previously with severity of WMH [34,36]. In the current study, lower phase shift was correlated with higher amounts of WMH and the effect size was quite large. The very strong correlation between hemodynamics and WMH suggests that autoregulatory dysfunction is one mechanism that promotes this aspect small vessel cerebrovascular disease among older adults. As WMH are associated with age-associated cognitive decline, motoric and emotional dysfunction, normalization of cerebral hemodynamic abnormalities may be one potential avenue for widespread preventative or therapeutic strategies among older adults. Our study extends this line of research by examining fibrillar amyloid, and further suggests that control of vascular factors may have therapeutic benefit for AD. Future work should employ longitudinal designs to examine the temporal emergence of autoregulatory dysfunction as it relates to amyloid deposition and small vessel cerebrovascular disease.

In conclusion, we showed an interrelationship among the severity of small vessel cerebrovascular disease, cerebral autoregulation, and fibrillar forms of amyloid.

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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.

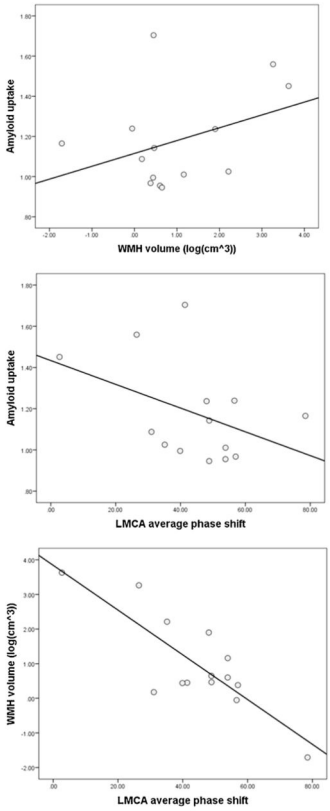

Fig. 1.

Correlations among WMH, amyloid uptake, and average phase shift. Top: correlation between WMH volume and mean amyloid SUVR value. Middle: correlation between average phase shift and amyloid SUVR value. Bottom: correlation between average phase shift and WMH volume.

Table 1

Descriptive statistics for phase shift, amyloid uptake SUVR, and WMH volumes for all participants.

	Mean	SD	Range
LMCA average phase shift	44.44	17.67	2.69–78.50
RMCA average phase shift	47.29	12.91	29.35–63.18
Amyloid uptake (mean SUVR)	1.18	0.24	0.95–1.70
WMH volume (log cm^3)	0.97	1.39	−1.71–3.63