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Characterizing the white matter hyperintensity penumbra with cerebral blood flow measures

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ABSTRACT

Objective: White matter hyperintensities (WMHs) are common with age, grow over time, and are associated with cognitive and motor impairments. Mechanisms underlying WMH growth are unclear. We aimed to determine the presence and extent of decreased normal appearing white matter (NAWM) cerebral blood flow (CBF) surrounding WMHs to identify 'WM at risk', or the WMH CBF penumbra. We aimed to further validate cross-sectional finding by determining whether the baseline WMH penumbra CBF predicts the development of new WMHs at follow-up.

Methods: Sixty-one cognitively intact elderly subjects received 3 T MPRAGE, FLAIR, and pulsed arterial spin labeling (PASL). Twenty-four subjects returned for follow-up MRI. The inter-scan interval was 18 months. A NAWM layer mask, comprised of fifteen layers, 1 mm thick each surrounding WMHs, was generated for periventricular (PVWMH) and deep (DWMH) WMHs. Mean CBF for each layer was computed. New WMH and persistent NAWM voxels for each penumbra layer were defined from follow-up MRI.

Results: CBF in the area surrounding WMHs was significantly lower than the total brain NAWM, extending approximately 12 mm from both the established PVWMH and DWMH. Voxels with new WMH at follow-up had significantly lower baseline CBF than voxels that maintained NAWM, suggesting that baseline CBF can predict the development of new WMHs over time.

Conclusions: A CBF penumbra exists surrounding WMHs, which is associated with future WMH expansion. ASL MRI can be used to monitor interventions to increase white matter blood flow for the prevention of further WM damage and its cognitive and motor consequences.

1. Introduction

White matter hyperintensities (WMHs) are common with age and grow over time (de Leeuw et al., 2001; Erten-Lyons et al., 2013; Maillard et al., 2012; Silbert et al., 2012). WMHs are commonly classified as periventricular (PVWMH) and deep (DWMH) lesions according to their locations and appearance. The volume of WMHs is associated with increased risk of cognitive (Au et al., 2006; Debette et al., 2010; DeCarli et al., 1995a; Longstreth et al., 1996; Silbert et al., 2008; Silbert et al., 2009) and motor (Silbert et al., 2008) impairment, stroke (Debette et al., 2010; Kuller et al., 2004; Wen and Sachdev, 2004), and mortality (Debette et al., 2010). Therefore, characterizing the growth of WMH volume over time has become an important research goal in order to impede the progression of clinical impairments. WMHs are likely ischemic in origin (Fazekas et al., 1993), specifically arteriolosclerosis (Erten-Lyons et al., 2013) and chronic hypoperfusion due to localization on the border zones of cerebral arteries (Kim et al., 2008). Yet the exact developmental process remains unclear.

The WMH penumbra is normal appearing white matter (NAWM) tissue surrounding WMHs that is more vulnerable than other healthy white matter (WM) to convert to WMHs (Maillard et al., 2011), or 'WM at risk'. A previous diffusion tensor imaging (DTI) study has shown that the WMH DTI-fractional anisotropy (FA) penumbra was approximately 3 mm from voxels comprised of WMHs (Maillard et al., 2011). Longitudinal studies also showed changes in baseline FA and FLAIR signal intensities in a WMH penumbra defined within 8 mm of WMH lesions (Maillard et al., 2014), which could predict incident

Abbreviations: WMH, white matter hyperintensity; PVWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; NAWM, normal appearing white matter; CBF, cerebral blood flow; PASL, pulsed arterial spin labeling; CASL, continuous arterial spin labeling; PCASL, pseudo-continuous arterial spin labeling; M_0, the initial ASL datasets; NAWM L1, normal appearing white matter layer 1; NAWM L15, normal appearing white matter layer 15.

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WMHs at follow-up (de Groot et al., 2013; Maillard et al., 2013). Another study also demonstrated the WMH penumbra as being a predilection site for new lacunes (Duering et al., 2013). While previous penumbra-defining methods capture current microstructural WM integrity disruption, arterial spin labeling can provide cerebral blood flow (CBF) information, which may serve to elucidate the etiology of WMH expansion prior to microstructural injury to the WM.

Pulsed arterial spin labeling (PASL) is capable of measuring WMH and NAWM cerebral blood flow. It has been shown previously that WMH CBF was significantly lower than NAWM CBF (Brickman et al., 2009). Therefore, lower CBF in the NAWM voxels surrounding WM lesions could be a suitable marker for indicating the WMH CBF penumbra. The aims of this study were to determine the presence and extent of low NAWM CBF surrounding WMHs to identify 'WM at risk', or the WMH CBF penumbra. We aimed to further validate cross-sectional findings by determining whether our previously identified baseline WMH CBF penumbra predicted the development of new WMHs at follow-up using longitudinal data. CBF delineation of the WMH penumbra could provide a potentially *modifiable* biomarker to identify 'at risk' tissue, for which interventions to prevent the accretion of WMH could be implemented.

2. Material and methods

2.1. Subjects

Sixty-one cognitively intact community dwelling elderly subjects currently participating in a Layton Aging and Alzheimer's Disease Center were recruited. Entry inclusion criteria included seniors aged 65 or above with a score of 0 on the Clinical Dementia Rating Scale (CDR) and ≥24 on the Mini-Mental State Examination. MRI exclusion criteria included a history of clinical stroke or evidence of cortical stroke on MRI, claustrophobia, inability to lie in a supine position for 90 min, and implanted metallic objects. All subjects signed written informed consent and approval from the Institutional Review Board of Oregon Health & Science University was obtained. All subjects received at least one brain MRI scan. Twenty-four subjects returned for a follow-up MRI. The mean (standard deviation, SD) interscan interval was 18 (11) months. Table 1 describes participant characteristics.

2.2. MRI sequences

Magnetic resonance imaging (MRI) data were obtained using a 3.0 T MRI scanner (TIM Trio System, Siemens Medical Solutions). Each subject underwent T_1-weighted magnetization prepared rapid gradient echo (MPRAGE), fluid attenuated inversion recovery (FLAIR), and QUIPSS II with thin-slice TI periodic saturation (Q2TIPS) PASL (Luh et al., 1999). T_1-weighted images were acquired using repetition time (TR) = 2300 ms, echo time (TE) = 3.4 ms, inversion time (TI) = 1200 ms, spatial resolution = 1 mm isotropic, and field of view (FOV) = 256 mm. Axial 2D FLAIR datasets were acquired using TR = 9000 ms, TE = 87 ms, TI = 2500 ms, FOV = 248 mm, slice thickness = 2 mm, and number of slices = 95. PASL sequence was obtained covering the basal ganglia inferiorly, through the centrum semiovale superiorly with following parameters: resolution = 3 × 3 × 4 mm, 2 mm gap, time between the inversion pulse and beginning of the periodic saturation pulse train 1 (TI_1) = 700 ms, the post-TI periodic saturation stop time (TI_{1S}) = 1600 ms, the time between the inversion pulse and the initial EPI read pulse (TI_2) = 1800 ms (Campbell and Beaulieu, 2006), TR = 3000 ms and TE = 13 ms. The sequence acquired 720 images in 3 separate runs. Subjects were instructed to stay awake with their eyes closed.

Table 1
Summary of participant characteristics at baseline.

Variables	Mean (SD)	Median	IQR
Number of subjects	61		
Age (years)	84.6 (8.0)	85.2	9
Female	48		
Percent number of subjects with history of hypertension	73%		
CDR	0	0	0
MMSE	28.9 (1.4)	29	2
Baseline total WMH volume (cc)	11.2 (9.5)	9.2	10.2
Baseline periventricular (PV) WMH volume (cc)	9.8 (9.1)	7.8	7.5
Baseline deep WMH volume (cc)	1.3 (1.4)	0.8	1.2
Baseline total brain NAWM volume (cc)	156.3 (36.3)	146.9	54.2
Baseline brain volume (cc)	837.0 (100.8)	818.2	115.6
Baseline intracranial volume (cc)	1860.3 (229.3)	1804.5	258.1

IQR = interquartile range; CDR = Clinical Dementia Rating Scale.

2.3. MRI processing

For each dataset, the T_1-weighted image was segmented into WM, gray matter (GM), and ventricle masks using FreeSurfer (v.5.1), and manually corrected for any tissue misclassification. The masks were then linearly aligned to the FLAIR image, and were later used to set the boundaries of the seed growing for the WMHs. To determine the WMH area, a histogram of the WM of FLAIR intensity was generated and the 45% above peak of the histogram was used as a cutoff to separate the WMH (>cutoff) and NAWM (<cutoff). Clusters of at least three voxels were used as seeds for a custom cluster-growing algorithm. For each cluster, the mean intensity was calculated and then all nearest neighbor voxels of intensity exceeding 95% of the mean cluster intensity were added to the cluster. The process was repeated until the cluster mean reached the lower limit of two standard deviations above the WM mean or until no additional voxels met the threshold. The WMH clusters were visually examined and manually corrected for accurate WMH coverage. WMH clusters contiguous with the ventricles were labeled periventricular WMHs (PVWMHs) and all others were considered deep WMHs (DWMHs).

To derive the subject-specific CBF map each of the three runs of PASL images was divided into labeled and controlled datasets. Each dataset was linearly aligned to the initial ASL datasets (M_0) and was inspected for the excessive head movement (≥2 mm or 2°). The area outside of the brain was excluded. The three runs were concatenated by linearly aligning the first and third runs to the second run. The M_0 from the three runs were averaged. Quantitative CBF was then calculated on a voxel basis according to Wang et al. (Wang et al., 2003). Voxel-wise partial volume correction was performed (Du et al., 2006).

To determine the WMH CBF penumbra, a NAWM layer mask for each individual dataset was created by linearly aligning the defined WMHs to the T_1-weighted image. Each layer was dilated away from the WMHs by 1 voxel (1 mm), for a total of 15 NAWM layers for PVWMH and DWMH separately, see Fig. 1A–B. The innermost layer, closest to WMH was layer 1 (NAWM-L1) and the outermost layer was layer 15 (NAWM-L15), see Fig. 1C. To prevent overlapping voxels between layers, before creating the next layer, the WMH and the previous NAWM layers were merged together to create a new 'seed'. To avoid the partial volume effects of the GM and CSF CBF, the GM and ventricular masks were dilated by 2 voxels, and subtracted from the NAWM layers. The NAWM layer mask was individually applied to the CBF map, which was previously linearly aligned to their T_1-weighted image and was resampled to 1 × 1 × 1 mm. Lastly, for each individual subject the mean CBF for WMHs and each NAWM layer was computed for PVWMH and DWMH separately, and compared with mean total brain NAWM CBF. Each mean value was adjusted for age.

For the longitudinal study, we focused only on the PVWMH as it was more prominent and consistent across subjects compared to DWMH (Table 1). To measure the CBF of the new PVWMH voxels at follow-up MRI, each individual's follow-up FLAIR image was linearly aligned to the same subject's baseline FLAIR image. The voxels with new PVWMHs