Characteristics of white matter hyperintensities in MR images of Cerebral Amyloid Angiopathy

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Purpose: MRI manifestations of cerebral amyloid angiopathy (CAA) are white matter hyperintensities (WMH) and cerebral micobleeds (CMB) [1-3]. Although the spatial distribution of CAA-related CMB has been established based on the pathological and imaging studies, the characteristics of CAA-related WMH have not been studied before. The purpose of this study was to study the volume and distribution of CAA-related WMH using an automated method for probability maps and voxelwise statistical maps of WMH on MRI.

Methods: MRI data were analyzed from 419 patients who were included from the nested MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) who were recruited from the general population [4]. Probable CAA and possible CAA were diagnosed using the previously validated Boston Criteria. Non-CAA was defined as CMB located in basal ganglia (deep gray matter) with or without additional CMB with a lobar, cortical, corticosubcortical, and infratentorial location and as CMB restricted to infratentorial region. Patients without CMB were assigned to no-MB group. All imaging was performed on an MR system operating at a field strength of 1.5 T (Philips Medical Systems, Best, The Netherlands). Dual fast spin echo, fluid attenuated inversion recovery (FLAIR), and susceptibility-weighted images were obtained from all patients. Segmentation of WMH, intracranial volume, and brain parenchyma volume was performed automatically using Software for Neuro-Image Processing in Experimental Research (SNIPER) [5], an in-house developed program for image processing. The volume of periventricular WMH and deep WMH was calculated automatically, and binarized mask images of WMH were also created for probability map.

The individual FLAIR volumes were registered to the Montreal Neurological Institute (MNI152) standard space using a two-steps registration procedure. Data was first linearly registered using FLIRT [6] and subsequently non-linearly adjusted using FNIRT, both tools available in the FMRIB Software Library (FSL). WMH mask images for each patient were transformed onto the MNI152 standard space using the parameters obtained from the aforementioned registrations. Sum of the registered WMH mask images of each group, normalized by the total number of datasets, provided White Matter Hyperintensities probability maps (WPM). Voxelwise statistics were carried out to study the differences between each pair of WPM maps obtained with the different groups. Each WPM gives WMH probability maps at each standard space voxel. Within these maps, the probability of finding a WMH in any given voxel is defined by the relative voxel intensity. Probability of the distributions observed from each WPM map being identical was tested as a Bernoulli process where a sequence of independent random variables, the corresponding voxel for each dataset, is taking values over two symbols, the presence or absence of WMH. Obtained p maps were subsequently thresholded at either p=0.01 or p=0.05.

Results: Of 419 subjects in this study, 105 (25.0%) were found to have CMB; moreover, these were divided into 3 groups according to the Boston Criteria: probable CAA, 32 (7.6%); possible CAA, 42 (10.0%); and non-CAA, 31 (7.4%). 314 patients (75.0%) without CMB were classified into no-MB group.

Table shows WMH characteristics in each group. There were between-group differences for total WMH (tWMH), subcortical WMH (sWMH), and periventricular WMH (pWMH) volumes: $\chi^2 = 21.8$, $p < 0.001$; $\chi^2 = 10.2$, $p = 0.013$; $\chi^2 = 24.6$, $p < 0.001$, respectively. Moreover we found significant increases of tWMH and pWMH volumes in both probable CAA and non-CAA, compared to no-MB ($p < 0.05$ and $p < 0.05$); however, none of the other inter-group differences were found. In patients with CMB, there were strong correlations between the total number of CMB and tWMH and pWMH volumes (r = 0.31, $p = 0.002$ for tWMH; r = 0.32, $p = 0.001$ for pWMH). These correlations were observed both in probable CAA or non-CAA.

In all groups, WMH were predominantly located at periventricular region, especially around anterior and posterior horn of the lateral ventricle (Figure 1). Voxelwise statistical maps with a threshold for a p-value of 0.05 were obtained comparing probable CAA and non-CAA vs. no-MB (Figure 2). As compared to non-CAA, increased WMH were observed the occipital periventricular white mateer in probable CAA.

Conclusion: Our study demonstrated that CMB are associated with WMH, and increased numbers are associated with increased volumes of WMH. Also we found evidence for differences in distribution of WMH associated with CAA-type CMB as compared to other types of CMB. These data suggest that 1) CMB and WMH are both manifestations of cerebral small vessel disease, and 2) WMH that are associated with CMB with a CAA-type distribution have a different distribution as compared to WMH associated with other CMB distributions.

Table

With and Without CMB		total	probable CAA	possible CAA	non-CAA	no-MB	p value
Number of patient, n (%)		419	32 (7.6)	42 (10.0)	31 (7.4)	314 (75)	
Age y, mean ± SD		77.3 ± 3	77.1 ± 3	77.5 ± 3	78.1 ± 3	77.2 ± 3	
WMH volume ml,mean ± SD	Total	7.14 ± 10.9	11.76 ± 11.7 *	8.51 ± 8.8	10.21 ± 9.7 *	6.19 ± 11.0	< 0.001
	Subcortical	1.54 ± 2.1	2.01 ± 2.2	1.84 ± 2.4	2.03 ± 1.9	1.41 ± 2.1	0.013
	Periventricular	5.60 ± 9.3	9.75 ± 10.1 *	6.65 ± 7.3	8.18 ± 8.4 *	4.78 ± 9.4	< 0.001
With CMB		total	probable CAA	possible CAA	non-CAA		
Number of patient, n		105	32	42	31		
Total number of CMB,		2.67 ± 3.5	3.28 ± 2.9	1.01 ± 0.3	4.16 ± 5.3		
Correlation with WMH volume r, p -value	Total	0.31, 0.002**	0.50, 0.004**	0.13, 0.40	0.67, < 0.001**		
	Subcortical	0.16, 0.99	0.27, 0.13	0.13, 0.40	0.27, 0.14		
	Periventricular	0.32, 0.001**	0.56, 0.001**	0.13, 0.40	0.69, < 0.001**		

WMH = white matter hyperintensities, CMB = cerebral microbleeds, r = correlation coefficient
* $p<0.05$ compared with no-MB by the Kruskal-Wallis test followed by the Mann-Whitney U test with Bonferroni correction
** $p<0.05$ by the Spearman's rank correlation test

Figure 1

Figure 2
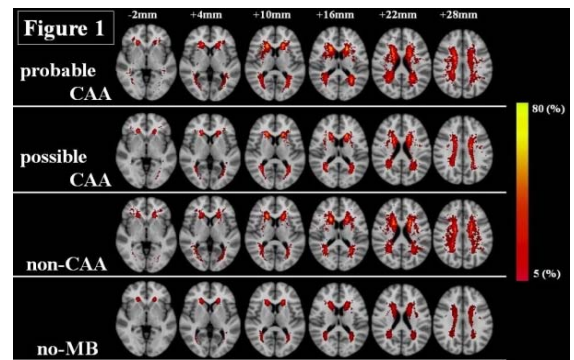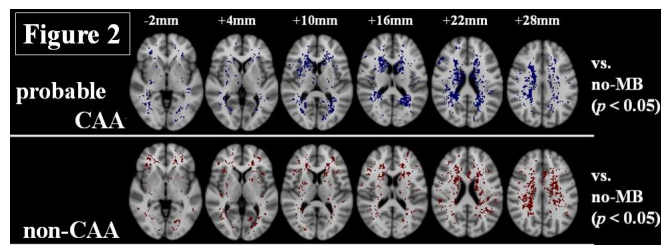
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