Staging cerebral amyloid angiopathy: from marker to model

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PART II

Novel MRI markers for cerebral amyloid angiopathy

5

INNOVATIVE MRI MARKERS OF HEREDITARY CEREBRAL AMYLOID ANGIOPATHY AT 7 TESLA

Chapter 5 | Innovative MRI markers of hereditary Cerebral Amyloid Angiopathy at 7 Tesla

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Stroke. 2018 Jun; 49(6): 1518–1520.

Abstract

Background and Purpose: The aim of the present study is to explore whether using 7 Tesla MRI, additional brain changes can be observed in Hereditary Cerebral Hemorrhage with Amyloidosis-Dutch type (HCHWA-D) patients as compared to the established MRI features of sporadic cerebral amyloid angiopathy (sCAA).

Methods: The local institutional review board approved this prospective cohort study. In all cases, informed consent was obtained. This prospective parallel cohort study was conducted between 2012 and 2014. We performed T_2^*-weighted MRI performed at 7 Tesla (7T) in pre-symptomatic mutation carriers (n=11, mean age 35 ± 12yrs), symptomatic HCHWA-D patients (n=15, mean age 45 ± 14yrs), and in control subjects (n=29, mean age 45 ± 14 yrs). Images were analyzed for the presence of changes that have not been reported before in sCAA and HCHWA-D. Innovative observations comprised intragyral hemorrhaging and cortical changes. The presence of these changes was systematically assessed in all participants of the study.

Results: Symptomatic HCHWA-D-patients had a higher incidence of intragyral hemorrhage (47% (7/15), controls 0% (0/29), $p<0.001$), and a higher incidence of specific cortical changes (40% (6/15) vs 0% (0/29), $p<0.005$). In pre-symptomatic HCHWA-D-mutation carriers, the prevalence of none of these markers was increased compared with control subjects.

Conclusions: The presence of cortical changes and intragyral hemorrhage are imaging features of HCHWA-D that may help recognizing sCAA in living patients.

Introduction

Sporadic cerebral amyloid angiopathy (sCAA) can only be diagnosed with certainty by means of post-mortem histological examination of the brain tissue. The Boston criteria, based on radiological findings, have been developed to help making the diagnosis sCAA during life.[1] New MRI markers may further improve these criteria. Hereditary Cerebral Hemorrhage with Amyloidosis- Dutch type (HCHWA-D), a hereditary form of CAA, is considered to be a good model for studying sCAA.[2]

Current disease markers for sCAA include hemorrhagic changes on CT or MRI, including the presence of intra cranial hemorrhage (ICH), lobar microbleeds (MBs), subarachnoid hemorrhage (SAH), and superficial siderosis.[3-6] In the pre-symptomatic phase of HCHWA-D, these markers are almost completely absent[7, 8] which may be due to the fact that hemorrhagic lesions are a late manifestation of the disease, or due to the limited sensitivity of conventional MRI systems in detecting the presence of more subtle hemorrhagic manifestations. High resolution T_2^*-weighted MRI at ultra-high field strength (7T) takes full advantage of the increased spatial resolution, increased signal-to-noise and contrast-to-noise ratio associated with high-field MRI, and could provide a sensitive method to detect early or small haemorrhagic lesions. The aim of the present study is to explore whether using 7 Tesla MRI, additional brain changes can be observed in HCHWA-D patients as compared to the established MRI features of sCAA.

Materials and Methods

The authors declare that all supporting data are available within the article (and its online supplementary files). The ethics committee of our institution approved the study, and written informed consent was obtained from all subjects. In total 15 symptomatic (mean age 55 years), and 11 pre-symptomatic HCHWA-D patients (mean age 35 years) and 29 controls (mean age 45 years) participated. At 7T T_2^*-weighed gradient echo scans were performed. Conventional markers were scored: ICH, MBs, SAH and superficial siderosis as previously described.[8] Based on prior visual inspection of the images by an experienced neuroradiologist, intragyral hemorrhaging and specific cortical changes were scored. Intragyral hemorrhaging is defined as a parenchymal hemorrhage restricted to the subcortical white matter of an individual gyrus (figure 1). A 'striped' cortical pattern is defined as linear hypointense stripes perpendicular to the cortex (figure 2). Please see *http://stroke.ahajournals.org* for supplementary information.

Statistics

Demographic characteristics were analyzed using post-hoc Mann-Whitney U-tests for MMSE score and age; for blood-pressure measurements a general linear model, univariate analysis adjusted for age and sex was performed; and for prevalence of cardiovascular risk factors and the differences in sex a chi-square test was used. For each marker prevalence, post-hoc univariate general linear modelling was used, adjusted for age and sex. For all dichotome features the interobserver variability (kappa value) was calculated. Please see *http://stroke.ahajournals.org*.

Results

The characteristics of the study cohort are shown in supplementary table I. No differences were found in these characteristics among pre-symptomatic, symptomatic mutation-carriers and control subjects, except for a significant difference between symptomatic HCHWA-D patients and pre-symptomatic carriers/controls in mean MMSE score and a significant difference in age between symptomatic patients and pre-symptomatic carriers, which is inherent to the disease.

Prevalence of all hemorrhagic markers are shown in table 1. Results (% of variance explained and FDR corrected p-values) of univariate general linear modelling for each MRI marker for detection of hereditary CAA are shown in supplementary table II. Symptomatic HCHWA-D patients had a higher incidence of intragyral hemorrhage (47% (7/15), controls 0% (0/29), $p<0.001$), and a higher incidence of the striped cortex sign (40% (6/15) vs 0% (0/29), $p<0.005$). This striped cortex was only observed in the

Table 1: Innovative MRI features and classic MRI markers for detection of hereditary CAA on T_2^*-w 7T MRI.

	Symptomatic carriers (n=15)	Pre-symptomatic carriers (n=11)	Controls (n=29)
Innovative Features			
Intragyral hemorrhage %	47 (7/15)	0 (0/11)	0 (0/29)
Striped cortex sign %	40 (6/15)	0 (0/11)	0 (0/29)
Classic Markers			
Lobar microbleeds %	100 (15/15)	18 (2/11)	7 (2/29)
Superficial siderosis %	93 (14/15)	9 (1/11)	0 (0/29)
ICH %	100 (15/15)	9 (1/11)	0 (0/29)
SAH %	47 (7/15)	18 (2/11)	0 (0/29)

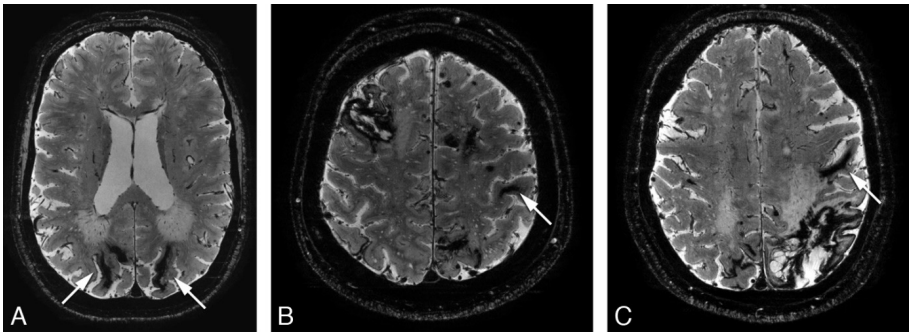
occipital lobe. In pre-symptomatic HCHWA-D mutation carriers, the prevalence of none of these markers was increased compared with control subjects.

The results of the distribution of the classic markers have been published previously.[8] Prevalence of all markers: ICH, MBs, SAH and superficial siderosis was increased in symptomatic HCHWA-D-patients ($p<0.001$), but not in pre-symptomatic mutation carriers.

The overlap; are patients positive for classic markers the same as the ones positive for the new markers, was also analysed. Patients with a striped cortex all showed microbleeds, 5/6 showed superficial siderosis, all showed ICHs, and 3/6 showed SAH. Of the patients with intragyral hemorrhage, all demonstrated microbleeds, all showed superficial siderosis, all showed ICHs, and 3/7 showed SAH. Of all symptomatic patients, three showed both intragyral hemorrhage and a striped cortex and all classic markers.

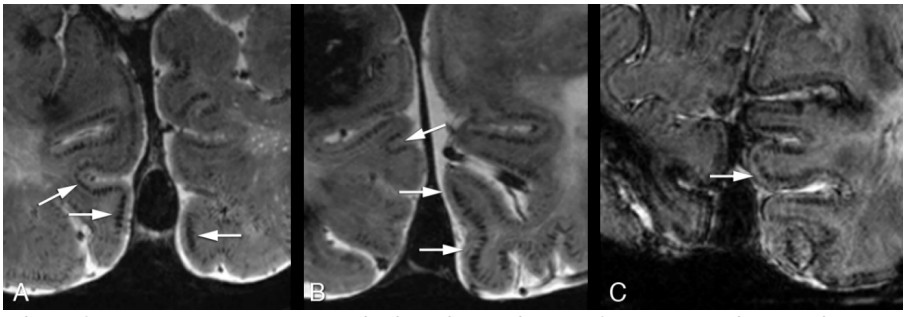
Interobserver agreement was calculated for the MRI markers. There was complete consensus concerning intragyral hemorrhaging ($\kappa = 1.0$). The κ value was substantial for a striped cortex, $\kappa = 0.74$ ($p<0.001$).

Figure 1: Intragyral hemorrhage.



High resolution 2D transverse T_2^*-weighted gradient echo 7 Tesla MRI scans showing intragyral hemorrhages (arrows) in three symptomatic patients.

Figure 2: Striped occipital cortex.



High resolution 2D transverse T_2^*-weighed gradient echo 7 Tesla MRI scans showing the striped cortex sign (arrows) in the occipital cortex of three symptomatic patients.

Discussion

Intragyral hemorrhage and a striped pattern in the occipital cortex at 7T MRI are imaging findings not detected earlier in HCHWA-D-patients, indicating innovative radiological manifestations of cerebral small vessel disease.

The striped cortex was found in 40% of the symptomatic mutation carriers and not in presymptomatic mutation carriers, which implicates that this marker is associated with more advanced stages of the disease. Interestingly, the striped cortex was only seen in the occipital lobe. The fact that in sCAA and HCHWA-D the occipital lobe is most severely affected with amyloidosis [2, 9, 10] may indirectly implicate that this cortical pattern may be a specific CAA marker. Given the shape and course in the cortex, they could be caused by Aβ deposition in and along the penetrating arteries co-locating with iron causing abnormal cortical patterns on T_2^*-weighted MRI.[11] Another explanation is the presence of calcification of the perforating cortical vessels which would also cause an hypointense signal on these images.[12, 13] The used MRI technique may be especially sensitive to deoxy hemoglobine in veins and also might explain the pattern we observed. Histological analysis of these radiological observations is required to elucidate the underlying histological substrate.

Intragyral hemorrhages are a hemorrhagic manifestation of CAA which has not yet been described previously. These hemorrhages are large enough to been seen in earlier sCAA studies, however the increased spatial resolution, signal-to-noise and contrast-to-noise of 7T MRI makes evaluation of the exact location of an hemorrhage much more precise. However, future research could focus on finding this pattern of hemorrhages in sCAA patients and the implication it could have for the diagnostic value of the Boston criteria.

We note several limitations of this study. These markers were only detected in the symptomatic stage and are not the most common markers. Still, we believe there is an added value of these markers. These markers might be specific for sporadic CAA, and could have added value to the specificity of the Boston criteria. Moreover, it gives us information on the disease process and therefore increase our understanding of sporadic CAA. Furthermore, our results were obtained in HCHWA-D patients, who have a particularly severe form of CAA and are small population as a whole which limits our sample size.

References

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Supplemental material

Supplemental methods

Participants

This prospective cohort study was conducted between 2012 and 2014. Subjects were selected via the HCHWA-D patient association in Katwijk, the Netherlands, (http://www.hchwa-d.nl) and the outpatient clinic of the Department of Neurology of the Leiden University Medical Center, based on DNA analysis for confirmation of codon 693 mutation in the amyloid-β precursor protein (AβPP) gene. Both symptomatic and pre-symptomatic mutation carriers were included. Subjects were considered symptomatic when they had experienced signs of the disease reported to a general practitioner. Control subjects were recruited from individuals at risk for HCHWA-D (i.e. one of the parents has HCHWA-D) but who tested genetically negative, and from subject spouses, family or friends, who also underwent genetic testing for inclusion. All controls were ascertained to be both stroke-free as well as receiving a negative genetic test. In this study only subjects who underwent 7T MRI were included. In total 55 participants were scanned: 26 were DNA-proven HCHWA-D mutation carriers of whom 15 were symptomatic, and 11 were pre-symptomatic. The mean age of the symptomatic subjects was 55 years, and 53% of them were women. The mean age of the pre-symptomatic subjects was 35 years, and 82% of them were women. In total 29 controls participated with a mean age of 45 years, of whom 59% were women. Demographics, vascular risk-factors, blood pressure and MMSE score were obtained at enrollment. The ethics committee of our institution approved the study, and written informed consent was obtained from all subjects.

MRI

Image acquisition

MRI was performed on a whole body human 7T MR-system (Philips Healthcare, Best, The Netherlands) using a quadrature transmit and 32-channel receive head coil (Nova Medical, Wilmington, MA, USA). Participants were scanned using a 2D flow-compensated transverse T_2^*-weighed gradient echo scan, with a total imaging duration of 20 minutes. Imaging parameters were: repetition time (TR)/echo time (TE) 794/25 ms, flip angle 45°, slice thickness 1.0 mm with a 0.1 mm interslice gap, 50 slices and coverage of 10 cm, 240

x 180 x 22 mm field-of-view (FOV), 1000 x 1024 matrix size – resulting in an in-plane spatial resolution of 0.24 x 0.24 mm^2. The bandwidth per pixel was 46 Hz, corresponding to a readout length of approximately 22 ms. The frequency and phase encoding directions were along the anterior-posterior and right-left axes, respectively. Shimming up to third order was performed using an image based shimming approach.[1]

Image analysis

Image analysis was performed on the T_2^*-weighed gradient echo scan. The following conventional markers were scored: ICH, MBs, SAH and superficial siderosis as previously described.[2] Based on prior visual inspection of the images by an experienced neuroradiologist (MvB (25 years of experience in neuroradiology)), the following changes were scored: intragyral hemorrhaging and specific cortical changes. For the detection of these potential markers the T_2^*-weighed gradient echo images were scored independently by two readers (EK (1 year of experience in neuroradiology)) and EvE (4 years of experience in neuroradiology)) blinded to clinical diagnosis. In the case of non-concordant scores a consensus reading was performed with a third experienced reader (SvR (10 years of experience in neuroradiology)).

Intragyral hemorrhaging is a subcategory of intracerebral hemorrhaging and is defined based on its location within the brain, namely as a parenchymal hemorrhage restricted to the subcortical white matter of an individual gyrus. By carefully investigating the surrounding MRI slices around the intragyral hemorrhage, it was checked if the hemorrhage was restricted to the subcortical white matter to avoid confusion with blooming superficial siderosis which would be presented as linear residues of blood in the superficial layers of the cortex. Examples are shown in figure 1. A 'striped' cortical pattern was found and is defined as linear hypointense stripes perpendicular to the cortex. Examples of this pattern are shown in figure 2.

Statistics

Where appropriate, data are expressed as mean and standard deviation. Significance level was set at 0.05 and all tests of significance were two-tailed. Demographic characteristics were analyzed using a Kruskal-Wallis test for the 3-group comparisons followed by a Mann-Whitney U-test for MMSE score and age; to be able to adjust for age and sex for comparison of blood-pressure measurements a general linear model, univariate analysis was performed; and for prevalence of cardiovascular risk factors and the differences in sex a chi-square test was used.

For each marker prevalence, univariate general linear modelling was used, adjusted for age and sex for the 3-group comparisons followed by an univariate general linear model adjusted for age and sex for post-hoc 2-group comparisons. R2 (% of variance explained) was reported so that the reader can interpret how well the model fits. P-values in the tables were FDR corrected. There is incomplete data for intragyral hemorrhages and a striped cortex sign for the comparison of the pre-symptomatic group versus controls because these features do not occur in both groups, so the model cannot be fit (also no significant results) (supplementary table II). For all dichotome features the interobserver variability (kappa value) was calculated and the grading of interobserver agreement was performed according to the recommendations of Landis and Koch.[3] All statistical analyses were performed with the Statistical Package of Social Sciences (SPSS, version 20.0; SPSS, Chicago, Ill).

Supplemental Table 1: Demographics and characteristics.

	Symptomatic carriers (n=15)	Pre-symptomatic carriers (n=11)	Controls (n=29)	p-value†
Mean Age (years) (SD)	55.1 (5.2)	34.6 (12.6)	44.7 (14.0)	0.005§
Sex (male/female)	7/8	2/9	12/17	0.398
Mean systolic blood Pressure (SD)	144.2 (19.8)	122.5 (11.4)	130.0 (26.8)	0.645
Mean diastolic blood Pressure (SD)	89.1 (10.4)	79.8 (9.6)	80.6 (10.4)	0.398
Mean arterial pressure (SD)	107.5 (12.4)	94.0 (8.6)	97.1 (15.1)	0.448
Hypertension (%)	40 (6/15)	0 (0/11)	17 (5/29)	0.090
Hyperlipidemia (%)	33 (5/15)	0 (0/11)	7 (2/29)	0.053
Diabetes mellitus (%)	7 (1/15)	9 (1/11)	0 (0/29)	0.398
Cardiovascular disease (%)	7 (1/15)	0 (0/11)	0 (0/29)	0.398
Mean MMSE* score (SD)	26.7 (3.8)	29.7 (0.6)	29.4 (0.7)	$p < 0.0001^{‡§}$

* *MMSE= mini mental state examination*

† *p-values were FDR corrected*

Significant differences indicated by: ‡, symptomatic vs. controls, P<0.05; §, symptomatic vs. pre-symptomatic, P<0.05

Supplemental Table 2: Results of univariate general linear modelling for each MRI marker for detection of hereditary CAA on T2*-w 7T MRI.

	R squared 3 groups comparison	p-value *	R squared sympt vs. controls	p-value *	R squared pre-sympt vs. controls	p-value *	R squared sympt vs. pre-sympt	p-value *
Innovative Features								
Intragyral hemorrhage %	0.718	p < 0.0001	0.710	p < 0.0001	-	-	0.665	0.162
Striped cortex sign %	0.396	p < 0.0001	0.377	p < 0.0001	-	-	0.286	0.176
Classic Markers								
Lobar microbleeds %	0.772	p < 0.0001	0.849	p < 0.0001	0.214	0.275	0.794	0.008
Lobar microbleeds %	0.772	p < 0.0001	0.849	p < 0.0001	0.214	0.275	0.794	0.008
Superficial siderosis %	0.844	p < 0.0001	0.911	p < 0.0001	0.106	0.291	0.752	0.008
ICH %	0.923	p < 0.0001	1.000	p < 0.0001	0.106	0.291	0.864	p < 0.0001
SAH %	0.313	0.001	0.406	p < 0.0001	0.237	0.249	0.160	0.900

* p-values were FDR corrected

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