NeuroImage: Clinical 11 (2016) 461–467

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Longitudinal decrease in blood oxygenation level dependent response in cerebral amyloid angiopathy

Aaron R. Switzer[a,d,e], Cheryl McCreary[b,e], Saima Batool[c,e], Randall B. Stafford[c,e], Richard Frayne[a,e], Bradley G. Goodyear[a,e], Eric E. Smith[a,e,*]

[a]Neuroscience Graduate Program, University of Calgary, Canada
[b]Department of Radiology, University of Calgary, Canada
[c]Department of Clinical Neurosciences, University of Calgary, Canada
[d]Hotchkiss Brain Institute, University of Calgary, Canada
[e]Seaman Family MR Research Centre, Foothills Medical Centre, Alberta Health Services, Canada

ARTICLE INFO

Article history:
Received 19 November 2015
Received in revised form 5 February 2016
Accepted 29 February 2016
Available online 3 March 2016

Keywords:
Cerebral amyloid angiopathy
Functional magnetic resonance imaging

ABSTRACT

Lower blood oxygenation level dependent (BOLD) signal changes in response to a visual stimulus in functional magnetic resonance imaging (fMRI) have been observed in cross-sectional studies of cerebral amyloid angiopathy (CAA), and are presumed to reflect impaired vascular reactivity. We used fMRI to detect a longitudinal change in BOLD responses to a visual stimulus in CAA, and to determine any correlations between these changes and other established biomarkers of CAA progression. Data were acquired from 22 patients diagnosed with probable CAA (using the Boston Criteria) and 16 healthy controls at baseline and one year. BOLD data were generated from the 200 most active voxels of the primary visual cortex during the fMRI visual stimulus (passively viewing an alternating checkerboard pattern). In general, BOLD amplitudes were lower at one year compared to baseline in patients with CAA ($p = 0.01$) but were unchanged in controls ($p = 0.18$). The longitudinal difference in BOLD amplitudes was significantly lower in CAA compared to controls ($p < 0.001$). White matter hyperintensity (WMH) volumes and number of cerebral microbleeds, both presumed to reflect CAA-mediated vascular injury, increased over time in CAA ($p = 0.007$ and $p = 0.001$, respectively). Longitudinal increases in WMH ($r_s = 0.04$, $p = 0.86$) or cerebral microbleeds ($r_s = -0.18$, $p = 0.45$) were not associated with the longitudinal decrease in BOLD amplitudes.

1. Introduction

Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of beta-amyloid in the media and adventitia of the leptomeningeal and cortical vasculature (Vinters, 1987). This pathology causes cerebral arterial bleeding and manifests as lobar intracerebral hemorrhages (ICH), cerebral microbleeds, subarachnoid hemorrhages, and superficial siderosis (Knudsen et al., 2001; Charidimou et al., 2012). CAA is also implicated as a cause of vascular cognitive impairment and dementia (MRC CFAS, 2001), which may be due in part to ischemic lesions caused by subsequent blood flow reduction (Greenberg et al., 2004; Smith et al., 2012).

Vascular beta-amyloid deposition has been shown to cause thickening of the vascular walls and loss of smooth muscle cells, thus impairing the vascular response to functional hyperemia (Davis-Salinas et al., 1995). Animal models of CAA have demonstrated impaired vascular reactivity in response to a vasodilatory challenge in CAA (Shin et al., 2007; Smith et al., 2008; Park et al., 2014). Cross-sectional functional magnetic resonance (fMRI) studies of CAA in humans have demonstrated delayed time-to-peak and reduced amplitude of the blood oxygenation level dependent (BOLD) responses to a visual stimulus (Dumas et al., 2012; Peca et al., 2013) even though clinical tests of visual function and visual evoked potentials were normal. Altered BOLD responses are typically more prominent within the occipital lobe compared to the frontal lobe, consistent with the preferential deposition of vascular beta-amyloid in posterior brain regions, a characteristic feature of CAA (Peca et al., 2013). In addition, the degree of reduction of BOLD response amplitude was strongly correlated with two markers of CAA-related brain injury: volume of white matter hyperintensity (WMH) of presumed vascular origin and the number of cerebral microbleeds

Abbreviations: BOLD, blood oxygenation level dependent; CAA, cerebral amyloid angiopathy; fMRI, functional magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery; ICH, intracerebral hemorrhages; SWI, susceptibility-weighted imaging; WMH, white matter hyperintensity.

* Corresponding author at: Ron and Rene Ward Centre for Healthy Brain Aging, Room 2941, Health Sciences Building, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada. Tel./fax: +1 403 944 1594.
E-mail address: eesmith@ucalgary.ca (E.E. Smith).

http://dx.doi.org/10.1016/j.nicl.2016.02.020

(Dumas et al., 2012; Peca et al., 2013). Thus reduced BOLD response amplitude in response to a visual stimulus may provide a potential in vivo biomarker of CAA severity.

Animal models of CAA show that vascular beta-amyloid accumulates over time, and is associated with progressive loss of vascular reactivity (Dubois et al., 2007); however, the timing and rate of cerebral hemodynamic impairment in patients with CAA is unknown because there are no published longitudinal studies to date.

The present study is designed to determine if BOLD FMRI can track the progression of the characteristic vascular reactivity impairment observed in CAA, using a one-year prospective longitudinal study design. We hypothesized that the BOLD response to a visual stimulus would decrease over one year in CAA, but remain unchanged in healthy similarly-aged controls. Additionally, we hypothesized that the decrease in BOLD response in CAA would be significantly associated with an increase in the volume of WMH of presumed vascular origin and the number of cerebral microbleeds, which are presumed to reflect the severity of CAA-related vascular injury.

2. Methods

2.1. Study population

Study participants included 22 patients with CAA and 16 non-cognitively impaired, stroke-free, healthy controls recruited as a part of a prospective longitudinal study. Patients presented with MR evidence of ICH, microbleeds, or superficial siderosis without other evident cause, consistent with the diagnosis of probable CAA by the validated Boston criteria (Knudsen et al., 2001; Linn et al., 2010). Specifically, the CAA population contained 12 patients that presented with ICH, 3 that presented with headache or cognitive impairment with neuroimaging evidence of CAA-related inflammation (all of whom were studied in a phase of remission without MRI FLAIR evidence of acute vasogenic edema at the time of study), 5 with cognitive symptoms without dementia, and 2 with transient focal neurological episodes. Three patients were recruited from a cognitive clinic and nineteen were recruited from a stroke prevention clinic. Patients were excluded if they resided in a nursing home or long-term care facility, had moderate to severe dementia (defined as a Clinical Dementia Rating (CDR) score > 1.0), had abnormal visual acuity (<20/50 Snellen visual acuity), or were not fluent in English (because English language cognitive testing was part of the study). Patients with recent symptomatic stroke (<90 days) were also excluded to avoid any acute effects of ICH. Patients with MRI evidence of ICH in the occipital pole were excluded if their hemorrhagic lesion extended into the occipital region of interest used to calculate the BOLD response amplitudes. Healthy controls were recruited from the community by advertising in a newsletter or poster, and did not have a history of stroke or dementia as determined by neurologist assessment. Each participant had a repeat study visit and MR imaging at one year. Subjects provided written consent to participate in the study, which was approved by our Institutional Review Board.

2.2. Measurements

All imaging was performed using a 3.0 Tesla MR scanner (either GE Signa VH/*i* or Discovery 750; GE Healthcare, Waukesha, WI) with a 12-channel phased-array neurovascular coil. Because of a MR scanner upgrade, 9 of the 22 patients with CAA and 10 of the 16 control subjects had their baseline scan on a GE Signa VH/*i* scanner and their one-year scan on a GE Discovery 750 scanner, while the remaining patients with CAA and control subjects had both baseline and one-year scans on the same GE Discovery 750 scanner. A T_2-weighted, two-dimensional fluid attenuated inversion recovery (FLAIR) sequence was used to measure the WMH of presumed vascular origin volume (TR/TE/TI = 9000/149/2250 ms, voxel size 0.9 × 0.9 × 3.5 mm, 39 slices, 3.5 mm slice thickness, 256 × 256 matrix size). Susceptibility-weighted imaging (SWI) was used to detect the number of cerebral microbleeds (TR/TE = 30/20 ms, voxel size 0.9 × 0.9 × 5 mm, 120 slices, 2 mm slice thickness, 256 × 256 matrix size). The entire imaging protocol took approximately 1 h and included diffusion tensor imaging and arterial spin labeling acquisitions that were not used in the present study.

All T_2*-weighted fMRI scans were acquired using a gradient-recalled echo, echo planar imaging (GRE-EPI) sequence (TR/TE = 2000/30 ms, voxel size 3.75 × 3.75 × 4 mm, 34 slices, 4 mm slice thickness, field of view = 240 × 240 mm). During fMRI scans, participants viewed four repetitions of 40-second blocks of an 8-Hz contrast-reversing checkerboard visual stimulus followed by 40 s of a grey screen with a central fixation cross.

2.3. Image analysis

All fMRI data were processed using the FMRIB Software Library (FSL version 5.0.1, Oxford, UK). Following brain extraction (Smith, 2002), fMRI data were corrected for interleaved slice timing, corrected for motion using the MCFLIRT tool (Jenkinson et al., 2002), spatially smoothed (using a 5-mm full-width half maximum Gaussian kernel) and temporally filtered using a high-pass temporal filter with a cutoff of 0.01 Hz. A voxel-by-voxel analysis of each participants fMRI data was then performed using a time-series General Linear Model (GLM) as implemented in the fMRI Expert Analysis Tool (FEAT) (Worsley, 2001) of FSL. The regressor of interest was a time-series model consisting of the binary timing of the visual stimulus convolved with a canonical hemodynamic response function. Estimates of brain activity magnitude in response to the stimulus were then computed using FEAT and converted to a *z*-statistic. The 200 most active voxels (11.3 cm^3) exhibiting the greatest *z*-statistic within the primary visual cortex were selected as the region of interest, and the amplitude of the BOLD response (calculated as the percent change in the MR signal between visual fixation and the checkerboard stimulus, as estimated using the *Featquery* tool of FSL) was compared across imaging sessions for each of the CAA and healthy control groups using a paired *t*-test for within-group changes and a two-sample *t*-test for between-group differences.

Due to the difference in prevalence of hypertension between the groups and the variation in MR scanner used between subjects, a mixed-model linear regression was used to determine whether association between CAA and longitudinal BOLD amplitude change over time was independent of age, sex, hypertension, or MR scanner. Because of our modest sample size, we used forward selection to serially enter and retain covariates significantly associated with the outcome, retaining only significant covariates ($p < 0.05$) or where there was evidence of confounding of the CAA group effect (defined as a 20% shift in the model beta-coefficient).

Because analyzing the most active voxels, in which the area of activation might differ between the baseline and one year scans, could minimize changes over time, we also performed a secondary analysis where we analyzed the BOLD amplitude changes in a pre-specified anatomically defined region of interest centered on the primary visual cortex, which is the brain region most heavily affected by vascular amyloid deposition. The anatomically defined visual cortex V1 region of interest (Amunts et al., 2000) was extracted from the Juelich Histological Atlas structures within FSL, and encompassed a 21.7 cm^3 volume of the primary visual cortex in Montreal Neurological Institute (MNI) space (Fig. 1). The anatomically defined ROI was coregistered into the fMRI space of each individual and the BOLD amplitude was calculated as an average of all voxels within the ROI.

In addition, each participant's preprocessed fMRI data set was registered to the standard MNI brain template to permit a voxel-by-voxel statistical analysis of the estimates of brain activity for each group across imaging sessions. This analysis was performed within FEAT using a mixed effects linear model, and the resulting comparisons between imaging sessions were computed as a *z*-statistic, with clusters of significantly activated voxels ($z > 2.3$) corrected for multiple comparisons at