Advanced MR image analysis in sporadic and Dutch-type hereditary Cerebral Amyloid Angiopathy

Schipper, M.R.

Chapter 3 | One-year follow-up of visually stimulated task-based fMRI in Dutch-type and sporadic Cerebral Amyloid Angiopathy

Manon R. Schipper[1], Maaike C. van der Plas[2], Emma A. Koemans[2], Kanishk Kaushik[2], Rosemarie van Dort[2], Reinier G.J. van der Zwet[2], Sanne E. Schriemer[2], Thijs W. van Harten[1], Sabine Voigt[1,2], Ingeborg Rasing[2], Marianne A.A. van Walderveen[1], Matthias J.P. van Osch[1], Marieke J.H. Wermer[3]

[1] Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands,

[2] Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands,

[3] Department of Neurology, University Medical Center Groningen, Groningen, The Netherlands

Based upon: *Benelux Chapter of the International Society of Magnetic Resonance in Medicine,* 2024.

Synopsis

Loss of vasoreactivity is the first manifestation of amyloid-β deposition in Cerebral Amyloid Angiopathy (CAA). To assess how vasoreactivity changes over time is important for designing treatment trials. In the current study, we studied visually stimulated task-based fMRI to assess vasoreactivity in pre-symptomatic (N = 5) and symptomatic Dutch-type CAA (N = 13) and sporadic CAA (N = 25) at baseline and one-year follow-up. The upslope of the BOLD response shows deterioration over time. However, changes in amplitude and time-to-peak are not above the noise level.

Impact

Assessing which markers in Cerebral Amyloid Angiopathy (CAA) change over a short time can indicate what markers to track during a treatment trial to determine if the treatment slows down disease progression.

Introduction

Cerebral Amyloid Angiopathy (CAA) is one of the leading causes of intracerebral hemorrhage in the elderly population. CAA is caused by vascular amyloid-β deposition, which leads to vessel rigidness and a resulting loss of vasoreactivity[81,20]. Subsequently, disease progression leads to non-hemorrhagic injury, cognitive impairment, and finally, hemorrhagic lesions[8]. The same temporal ordering can be recognized in Dutch-type CAA (D-CAA)[118]. D-CAA is an autosomal hereditary variant of CAA that is pathologically, biochemically, and radiologically very similar to sporadic CAA (sCAA) and enables a definitive diagnosis through genetic testing and thereby studying the pre-symptomatic disease stage[119]. Previous research assessing vasoreactivity through visually stimulated task-based fMRI – where amplitude and time-to-peak (TTP) are used as measures to assess the size and timing of the response – has shown a decrease in amplitude in sCAA over a one-year follow-up[19]. In D-CAA, the amplitude and TTP are reduced in pre-symptomatic D-CAA but not in symptomatic D-CAA over a four-year follow-up[110]. With the current study, we aimed to assess one-year follow-up differences in amplitude, TTP, and upslope in pre-symptomatic and symptomatic D-CAA and sCAA as part of a larger study to assess one-year follow-up radiological markers in these cohorts.

Methods

For the assessment of vasoreactivity, we included 5 pre-symptomatic D-CAA (mean age 44 years, range 35-56y), 13 symptomatic D-CAA (mean age 61y, range 47-74y), and 25 sCAA (mean age 70y, range 62-84y). Participants were considered to be symptomatic when they had a symptomatic hemorrhage. Vasoreactivity was assessed through visually stimulated task-based fMRI[1]. Blood-oxygen-level-dependent (BOLD) fMRI (TR = 1500ms, TE = 38ms, FOV = 210x177x59mm^3, voxel size = 2.50x2.50x2.81mm^3, and 224 dynamics) was acquired with a visual stimulus paradigm that consisted of seven 20s blocks of an 8 Hz flashing radial checkerboard, followed by a grey screen for 28s[81]. BOLD data was processed with FSL's FEAT v6.0[90], as previously described[120]. The pre-processed fMRI data were analyzed within the primary visual cortex[94], and intracerebral hemorrhage and surrounding gliosis were removed from the ROI when there was overlap. A trapezoid fit was applied to the averaged BOLD response per participant to determine amplitude and TTP[81]. The upslope was calculated by dividing the amplitude by the TTP. If the BOLD response was too minimal for a trapezoid fit

to be applied, the timing parameter was not included for further analysis, and the upslope was set to zero. In these cases, the amplitude was calculated as the maximum of the BOLD response (after outlier exclusion of more than 3 median absolute deviations from the median) minus the baseline.

Results

The amplitude, TTP, and upslope for the three groups are presented in Figures 1 and 2, respectively. The data shows substantial variation over a one-year follow-up rather than a clear deterioration. With the upslope, which combines the amplitude and the TTP, a clearer deterioration could be observed in all groups, which is supported by the visualization in Figure 4. Figures 3 and 4 show the one-year follow-up measure as function of the baseline measure. These figures do not show a clear relation in amplitude and TTP at baseline compared to follow-up.

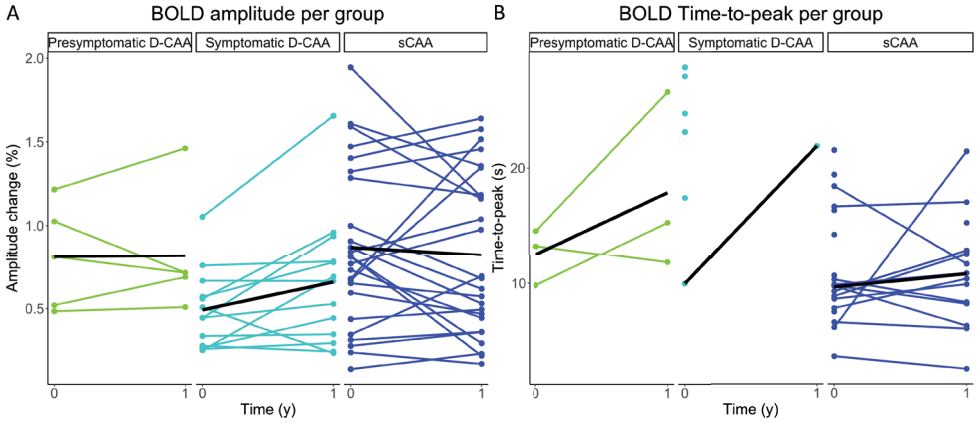

Figure 1. BOLD parameters a) amplitude change compared to the baseline and b) time-to-peak, over one-year follow-up in pre-symptomatic Dutch-type CAA, symptomatic Dutch-type CAA, and sporadic CAA.

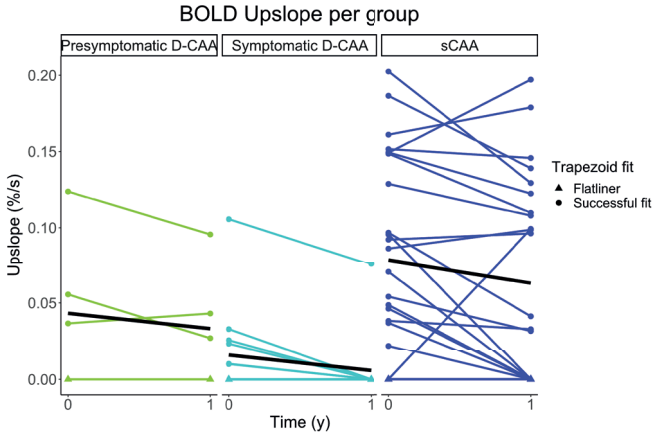

Figure 2. BOLD parameter upslope, calculated as amplitude change divided by time-to-peak, over one-year follow-up in pre-symptomatic Dutch-type CAA, symptomatic Dutch-type CAA, and sporadic CAA.

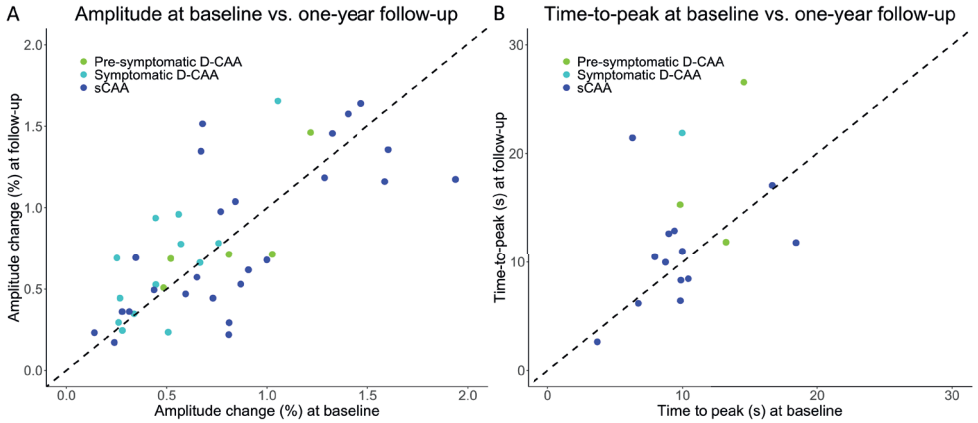

Figure 3. BOLD parameters a) amplitude change and b) time-to-peak, with the follow-up measure as function of the baseline measure.

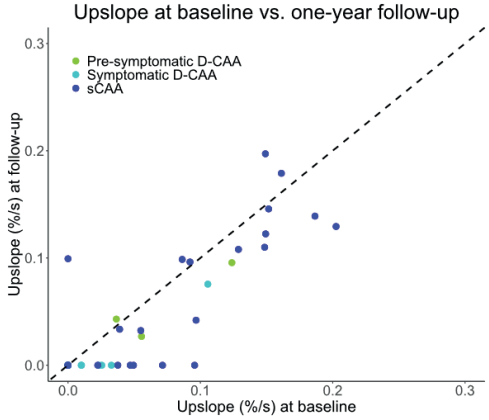

Figure 4. BOLD parameter upslope, calculated as amplitude change divided by time-to-peak, with the follow-up measure as function of the baseline measure.

Discussion

In the current study, we do not observe a clear deterioration in the BOLD parameters amplitude and TTP. When combining amplitude and TTP, by looking at the upslope, we observed a clearer deterioration over a one-year follow-up. A possible explanation for not observing a clearer deterioration may be that we mostly look at patients and D-CAA mutation carriers who are probably already in a further stage of the disease process, i.e. already suffering from significant vasoreactivity reduction at baseline measurement. Since vasoreactivity is the first manifestation after amyloid-β deposition, vasoreactivity may be most noticeable in D-CAA mutation carriers in the earliest disease stage. This would align with previous results showing deteriorated vasoreactivity over a four-year follow-up in younger pre-symptomatic, but not in symptomatic D-CAA[110].

Conclusion

The upslope parameter showed the clearest deterioration of vasoreactivity over a one-year follow-up in pre-symptomatic, symptomatic D-CAA and sCAA. We observed more variation over time in the amplitude and the TTP, perhaps explaining why a clear deterioration was not observed. For future research, it would be interesting to include younger participants in the study who are still in an earlier stage of the disease process to see if younger D-CAA mutation carriers show a more apparent decrease at one-year follow-up.