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Delayed arrival of arterial blood in cortex is associated with decreased CSF levels of amyloid beta in predementia Alzheimer's disease

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Background and aims: Brain amyloid-beta 1-42 (Abeta42) clearance is partly by drainage along basement membranes of capillaries and arteries. This mechanism may deteriorate with age and protein deposition, especially in APOEe4 carriers. Arterial spin labeling-MRI (ASL) is a non-invasive method measuring cerebral blood flow (CBF), and the CBF spatial coefficient of variation (CoV) is a putative proxy for arterial skull-base to capillary transit time (ATT) (1). A prolonged ATT is related to cardiovascular risk factors and ischemic disease. The aim of this study was to investigate whether CoV is related to CSF Abeta42 levels.

Methods: Predementia cases and controls from the Norwegian DDI-study (n=113, age=63.1y, m/f=47/66) had MRIs, blood sampling, lumbar puncture, and cognitive assessments, with two-year follow-up. ASL measures (2D-pCASL on 3T-Achieva or 3T-Ingenia scanners) were analyzed using ExploreASL. Abeta42 and the reciprocal of CoVs (sequentially for mean cortex, frontal, parietal, occipital and temporal cortices) for 143 observations were entered as dependent and independent variables, respectively, in a linear mixed model with random intercept for subjects, adjusting for age, APOEe4 and the interaction of age and APOEe4.

Results: CSF Abeta42 was significantly associated with (the reciprocal of) mean cortex CoV (B=124, p=0.028).

Conclusion: We show a relation between increased amyloid deposition and prolonged ATT, with decreased Abeta42 levels in CSF and mean cortex spatial CoV of CBF, respectively. These results are in line with the hypothesis of impaired Abeta42 clearance along peri-arterial drainage pathways in compromised vasculature.

Table 1. Demographical data. Age and $A\beta_{1-42}$ are described with mean and standard deviation, and mean cortex spatial CoV with median and interquartile range.

	Total	Normal control	Control with abnormal cognitive screening	Subjective cognitive decline (SCD)	Mild Cognitive Impairment (MCI)
	N=143	N=45	N=12	N=59	N=27
Female	86 (60.1%)	26 (57.8%)	7 (58.3%)	40 (67.8%)	13 (48.1%)
Age	63.1 (8.2)	62.8 (8.9)	63.3 (9.2)	62.6 (7.2)	64.7 (8.8)
APOEε4 carriers	54 (37.8)	12 (26.7%)	4 (33.3%)	27 (45.8%)	11 (40.7%)
$A\beta_{1-42}$ (pg/ml)	1058 (214)	963 (200)	975 (289)	883 (358)	982 (280)
Mean cortex spatial CoV	0.43 (0.08)	0.43 (0.09)	0.46 (0.22)	0.42 (0.07)	0.42 (0.12)

1. Mutsaerts et al. J Cereb Blood Flow Metab. 2017

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