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Brain volume and white matter hyperintensities as determinants of cerebral blood flow in Alzheimer's disease

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ABSTRACT

To better understand whether decreased cerebral blood flow (CBF) in patients with Alzheimer's disease (AD) reflects neurodegeneration or cerebral small vessel disease, we investigated the associations of normalized brain volume (NBV) and white matter hyperintensity (WMH) volume with CBF. We included 129 patients with AD (66 ± 7 years, 53% female) and 61 age-matched controls (64 ± 5 years, 43% female). CBF was measured with pseudocontinuous arterial spin labeling at 3T in the whole brain and in partial volume corrected cortical maps. When NBV and WMH were simultaneously entered in age and sex adjusted models, smaller NBV was associated with lower whole brain (Stβ: 0.29; $p < 0.01$) and cortical CBF (Stβ: 0.28; $p < 0.01$) in patients with AD. Larger WMH volume was also associated with lower whole brain (Stβ: −0.22; $p < 0.05$) and cortical CBF (Stβ: −0.24; $p < 0.05$) in AD. Additional adjustments did not change these results. In controls, neither NBV nor WMH was associated with CBF. Our results indicate that in AD, lower CBF as measured using pseudocontinuous arterial spin labeling, reflects the combined disease burden of both neurodegeneration and small vessel disease.

1. Introduction

Alzheimer's disease (AD) is essentially regarded as a neurodegenerative disease, characterized by the accumulation of amyloid plaques and neurofibrillary tangles that eventually leads to brain atrophy (Jack et al., 2010). Increasing evidence indicates that AD patient not only have brain volume loss, but also often have an altered cerebral blood flow (CBF). Although some studies report relative regional increases in (early) AD (Alsop et al., 2008; Dai et al., 2009), the most consistent finding is a decrease in absolute CBF in patients with AD (Alexopoulos et al., 2012; Alsop et al., 2010; Binnewijzend et al., 2013). This decreased CBF is in general assumed to be a reflection of the neurodegenerative process (Wolk and Detre, 2012).

Lower CBF in AD patients may not only relate to neurodegeneration, but may also be associated with small vessel disease (SVD). White matter hyperintensities (WMH) of presumed vascular origin are a commonly used magnetic resonance imaging (MRI) marker to indicate the presence of SVD (Wardlaw et al., 2013). WMH are assumed to result from ischemia and they are more prevalent in AD patients compared with the general elderly population (Scheltens et al., 1995). Previous studies have shown that WMH are associated with lower CBF as well (Bastos-Leite et al., 2008; Schuff et al., 2009; Vernooij et al., 2008).

CBF can be measured by arterial spin labeling (ASL); a functional MRI technique that uses magnetically labeled arterial blood water as an endogenous tracer (Petersen et al., 2006). The pseudocontinuous variant of ASL (PCASL) uses a multitude of millisecond-long pulses to achieve a high labeling efficiency and effective compensation of magnetization transfer effects (Dai et al., 2008).

Neurodegeneration and SVD are common in patients with AD, but to our knowledge, no previous studies have investigated how both processes relate to the generally described decreased CBF. Our aim was to explore whether independent relationships exist between normalized brain volume (NBV) or WMH on the one hand and CBF on the other hand. We hypothesized that the lower CBF in AD is not only reflective of the neurodegenerative process, but that

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CBF may be even further decreased when SVD is present. The well-characterized Amsterdam Dementia Cohort with PCASL measurement allowed us to investigate the determinants of CBF in AD patients and controls.

2. Methods

2.1. Subjects

Subjects for this study were drawn from the memory clinic based Amsterdam Dementia Cohort. We included 129 AD patients and 61 age-matched controls who visited our memory clinic between October 2010 and June 2012. All subjects underwent an extensive dementia screening, including medical history, neurologic, and physical examination, cognitive assessment, and brain MRI. The diagnosis "probable AD" was made according to the NINCDS-ADRDA criteria, by consensus of a multidisciplinary team and all patients fulfilled the core clinical criteria of the NIA-AA (McKhann et al., 1984, 2011). The control group consisted of age-matched control subjects, who presented with cognitive complaints, but for whom clinical investigations were normal and criteria for mild cognitive impairment (Petersen et al., 2001), dementia, or any other neurologic or psychiatric disorder were not met. As subjective complaints may represent preclinical AD in a subgroup (Sperling et al., 2011), we only included subjects with normal cerebrospinal fluid (CSF) Aβ42 levels (see Mulder et al. (2010) for a detailed description of CSF analyses). For all subjects, the presence of hypertension, hypercholesteremia, and diabetes mellitus were determined based on self-reported medical history and medication use. Smoking status was defined as never, former, or current. Blood pressures were measured manually using a sphygmomanometer. Exclusion criteria were the presence of structural brain lesions and failure of preprocessing of the MRI scans. The ethical review board of the VU University Medical Center approved the study. We obtained informed consent from all patients to use their clinical data for research purposes.

2.2. MRI protocol

MRI of the brain was acquired on a 3T whole body MR system (Signa, HDxt, General Electric Medical Systems, Milwaukee, WI, USA), using an 8-channel phased-array head coil. The MRI protocol included a sagittal 3D T1-weighted sequence (IR-FSPGR, repetition time [TR] = 7.8 ms, echo time [TE] = 3 ms, inversion time = 450 ms, flip angle = 12°, voxel sixe = 1.0 × 0.9 × 0.9 mm), a sagittal 3D fluid-attenuated inversion-recovery (TR = 8000 ms, TE = 123.6 ms, inversion time = 2350 ms, voxel size = 1.0 × 1.0 × 1.0 mm) an axial 2D T2* gradient-echo with an echo-planar read-out (EPI: TR = 5300 ms, TE = 25 ms, voxel size = 1.0 × 0.5 × 0.5 mm), and an axial 2D proton density/T2-weighted fast spin echo (PD-T2: TE = 20/112 ms, TR = 8680 ms, voxel size = 1.0 × 0.5 × 0.5 mm). PCASL perfusion images (3D-FSE acquisition with background suppression, post-label delay = 2.0 seconds, TR = 4.8 seconds, TE = 9 ms, spiral readout = 8 arms × 512 samples; voxel size = 1.0 × 1.7 × 1.7 mm) were calculated using a single compartment model (Buxton et al., 1998) after the subtraction of labeled images from control images. Binnewijzend et al. (2013) provides a more detailed description of the ASL sequence.

2.3. PCASL cerebral blood flow measures

After correcting T1-weighted and PCASL images for gradient nonlinearities in all the 3 directions, data-analyses were carried out using FSL (version 4.1.9; http://www.fmrib.ox.ac.uk/fsl). Preprocessing of T1-weighted images consisted of removal of non-brain tissue (Smith, 2002), linear registration to standard space (Jenkinson and Smith, 2001), and tissue segmentation (Zhang et al., 2001) yielding partial volume estimates. PCASL images were linearly registered to the brain-extracted T1-weighted images. Partial volume estimates were transformed to the ASL data space and used in a regression algorithm (Asllani et al., 2008) using a Gaussian kernel of 9.5 mm full width at half maximum, to create partial volume corrected (PVC) cortical CBF maps. Mean whole brain CBF was calculated using the segmented brain mask. Mean cortical CBF was calculated using the partial volume estimates as a weighting factor. CBF was defined in mL/100 g/min.

2.4. Normalized brain volumes

NBV (mL) was estimated with the SIENAX software tool (Smith, 2002), part of FSL, using optimized brain extraction tool options as described previously (Popescu et al., 2012). To avoid lesion-associated segmentation biases, before segmentation lesions were filled with intensities of the normal appearing white matter using the automated lesion-filling technique LEAP (Chard et al., 2010).

2.5. White matter hyperintensities

WMH were segmented using a locally developed *k*-Nearest Neighbor algorithm (Steenwijk et al., 2013) based on a previous work (Anbeek et al., 2008). In short, this algorithm uses fluid-attenuated inversion-recovery and T1 tissue intensity, spatial information, and tissue priors to compare the brain voxels of a newly presented data set to a collection of manually labeled examples in a feature space. Based on the most similar examples, the probability of a voxel being a lesion is computed and thresholded to obtain a binary lesion segmentation. Importantly, the training set for automated lesion segmentation was generated on images acquired with the same scanner and pulse sequences as those in the present study. All segmentations were visually inspected. WMH volumes (in milliliter, mL) were normalized for head size by multiplying the volumes by a scaling factor, derived from the SIENAX estimation.

2.6. Other MRI measures

Left and right hippocampal volumes (mL) were quantified using FSL FIRST (FMRIBs Integrated registration and segmentation tool) (Patenaude et al., 2011). All segmentations were visually inspected. Hippocampal volumes were normalized for head size by multiplying the volumes by the SIENAX derived scaling factor. For analytical purposes, left and right hippocampal volumes were summed. Cerebral microbleeds were visually assessed and defined as small round foci of hypointense signal, up to 10 mm in brain parenchyma on T2*-weighted images. Microbleed count was dichotomized as present or absent. Lacunes (of presumed vascular origin) were defined as deep lesions (3–15 mm), with CSF-like signal on all sequences; they were scored as present or absent.

2.7. Data analysis

Statistical analyses were performed using SPSS (version 20; SPSS, Chicago, IL, USA). As WMH volumes were not normally distributed, we used log-transformed values. Differences in baseline characteristics between groups were investigated with Student t-test for continuous variables and χ^2 test for dichotomous variables. Differences in CBF between groups were analyzed using 1-way analysis of covariance, corrected for age and sex. Linear regression analysis was carried out to investigate the associations of NBV and WMH (independent) with CBF (dependent). All models were adjusted for age and sex. In model I, we investigated the univariate associations of NBV or WMH with CBF. In model II, NBV and WMH were