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Featured Article

Lower cerebral blood flow is associated with impairment in multiple cognitive domains in Alzheimer's disease

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Abstract

Introduction: We examined the association between decreased cerebral blood flow (CBF) and cognitive impairment in Alzheimer's disease (AD), mild cognitive impairment (MCI), and subjective cognitive decline (SCD).

Methods: We included 161 AD, 95 MCI, and 143 SCD patients from the Amsterdam Dementia Cohort. We used 3-T pseudo-continuous arterial spin labeling to estimate whole-brain and regional partial volume–corrected CBF. Neuropsychological tests covered global cognition and five cognitive domains. Associations were investigated using linear regression analyses.

Results: In the whole sample, reduced overall and regional CBF was associated with impairment in all cognitive domains. We found significant interactions between diagnosis and CBF for language and between diagnosis and parietal CBF for global cognition and executive functioning. Stratification showed that decreased CBF was associated with worse performance in AD patients but not in MCI or SCD.

Discussion: Our results suggest that CBF may have potential as a functional marker of disease severity.

Keywords: Brain perfusion; Dementia; Alzheimer's disease; Arterial spin labeling; Cognition

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease that causes dementia. Hallmark of AD is severe cognitive impairment with interference in daily living. In addition to structural brain changes such as volume loss, AD patients have decreased cerebral blood flow (CBF) [1–3]. Regional CBF mapping can be accomplished with magnetic resonance imaging (MRI)–based arterial spin labeling (ASL). ASL is a noninvasive MRI technique that uses magnetically labeled water as a tracer for blood flow.

Decreased CBF is thought to reflect neuronal dysfunction and synaptic failure, the latter is considered to be the best correlate of cognitive decline in AD [4–7]. Decreased CBF as a reflection of synaptic failure is possibly one of the determinants of cognitive impairment. In a former study, we found that in mild cognitive impairment (MCI) and AD patients, lower ASL-measured CBF was related to more severe global cognitive impairment (measured with the Mini-Mental State Examination [MMSE]) [3]. Several

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previous studies have investigated the association between CBF and cognitive impairment and found a relationship between lower CBF and worse cognitive performance [3,8–11]. Comparability is hampered, however, by small sample sizes and the use of only a cognitive screening test or a few neuropsychological tests to evaluate cognitive impairment.

Based on the earlier findings, we hypothesized that whole-brain and regional CBF would correlate with cognitive functioning in a memory clinic population. We expected this association most prominently in AD providing support for ASL-CBF as a measure for disease severity. To test this hypothesis, we investigated the associations between ASL-CBF and performance in specific cognitive domains in a large sample of patients with subjective cognitive decline (SCD), MCI, and AD using an extensive and standardized neuropsychological test battery.

2. Methods

2.1. Subjects

We included 399 patients (143 SCD, 95 MCI, and 161 AD patients) with available ASL and standardized neuropsychological assessment from the memory clinic–based Amsterdam Dementia Cohort [12]. All patients visited our memory clinic between October 2010 and November 2012 and underwent standardized brain MRI at 3T, organized in a 1-day standardized dementia screening that included medical history, physical and neurological examinations, screening laboratory tests, and neuropsychological assessment. Clinical diagnosis was established by consensus in a multidisciplinary team [12]. AD patients met the NINCDS–ADRDA criteria (proposed by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) for probable AD [13] and also met the core clinical criteria for probable AD proposed by the National Institute on Aging-Alzheimer's Association (NIA–AA) workgroup [14]. Diagnosis of MCI was based on the Petersen and NIA–AA criteria for MCI [15,16]. Patients were considered to have SCD when they presented with cognitive complaints, and results of clinical assessments were normal (i.e., criteria for MCI or psychiatric disorder were not fulfilled and other underlying neurological or psychiatric diseases were ruled out) [17,18].

For all patients, the presence of vascular risk factors (i.e., hypertension, hypercholesterolemia, and diabetes mellitus) was determined based on self-reported medical history and medication use. Smoking status was defined as never, former, or current. Level of education was classified according to the system of Verhage ranging from 1 to 7 (low to highly educated) [19]. The study was approved by the medical ethics committee of the VU University Medical Center. All patients provided written informed consent for their clinical data to be used for the research purposes.

2.2. Neuropsychological assessment

Cognitive functioning was assessed by a standardized neuropsychological test battery. We assessed global cognition and five cognitive domains. For global cognition, we used the MMSE [20]. For memory, we used the Visual Association Test (VAT) and the total immediate recall and delayed recall of the Dutch version of the Rey Auditory Verbal Learning Test [21,22]. To examine language, we used the VAT naming, category fluency (animals), the Dutch version of the Controlled Oral Word Association Test (letter fluency), and the comparative questions and naming condition of the Arizona Battery for Communication Disorders [21,23–26]. For attention, we used the Trail Making Test (TMT) part A, the Letter Digit Substitution Test, the forward condition of the Digit Span, and the Stroop Test card I and II [27–30]. To examine executive functioning, we used the TMT part B, the backward condition of the Digit Span, Stroop Test card III, and the Frontal Assessment Battery [27–29,31]. To assess visuospatial functioning, we used three subtests of the Visual Object and Space Perception battery: (i) incomplete letters, (ii) dot counting, and (iii) number location [32].

Neuropsychological data were standardized into z-scores. TMT A and B and the Stroop Test scores were log transformed because of non-normal distribution and inverted by computing $-1 \times z$-score, so that higher scores imply a better performance. In patients where the TMT B was aborted ($n = 81$), we estimated TMT B by multiplying the time needed to complete TMT A with the mean B/A index. The mean B/A index for all patients who completed both TMT A and B ($n = 318$) was 2.99. On the other tests, 1%–11% of the test scores were missing, and these scores were not imputed. To create the five cognitive domains (i.e., memory, language, attention, executive functioning, and visuospatial functioning), mean z-scores of the completed tests in every domain were calculated.

2.3. MRI protocol

MRI was performed on a 3-T whole-body MR system (Signa HDxt; GE Medical Systems, Milwaukee, WI, USA) using an eight-channel head coil. The MRI protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and gradient-echo T2*-weighted images. Global cortical atrophy (GCA) was defined on axial FLAIR images (range: 0–3) [33], and the severity of white matter hyperintensities (WMHs) using the Fazekas scale was determined on the FLAIR sequence (possible range: 0–3) [34], both were dichotomized into absent (0–1) or present (2–3). Medial temporal lobe atrophy (MTA) was determined on coronal T1-weighted images using the Scheltens scale (range: 0–4) [35], and the mean of left and right MTA scores were dichotomized into MTA absent (<1.5) or MTA present (≥ 1.5). Lacunes were defined as deep lesions (3–15 mm)