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Featured Article

Cerebral hypoperfusion is not associated with an increase in β-amyloid pathology in middle-aged or elderly people

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Abstract

Introduction: It is hypothesized that cerebral hypoperfusion promotes the development of Alzheimer pathology. We therefore studied whether longstanding cerebral hypoperfusion is associated with Alzheimer pathology in nondemented humans.

Methods: Cerebral blood flow and β-amyloid (^{18}F-Flutemetamol) positron emission tomography retention were assessed in eleven patients with unilateral occlusion of precerebral arteries resulting in chronic and uneven hypoperfusion. A subset of patients underwent tau (^{18}F-AV-1451) positron emission tomography.

Results: The blood flow was significantly reduced on the affected side of the brain in patients with unilateral occlusion of the internal carotid artery or stenosis of the middle cerebral artery. However, the cortical uptake of ^{18}F-Flutemetamol or ^{18}F-AV-1451 was not altered.

Discussion: Our results suggest that longstanding cerebral hypoperfusion in humans does not result in accumulation of β-amyloid fibrils or tau aggregates.

Keywords: Cerebral hypoperfusion; β-amyloid; Alzheimer's disease; Pathogenesis; Tau

1. Background

Alzheimer's disease (AD) is the most common cause of dementia, with a prevalence of 5–6% in the population older than 60 years in Western Europe and North America [1]. AD is neuropathologically characterized by the presence of β-amyloid plaques and tau-containing neurofibrillary tangles [2]. β-amyloid accumulation is believed to be the crucial mechanism in AD, starting decades before clinical symptoms, and the presence of β-amyloid seems to be a prerequisite for the spread of tau outside the transentorhinal/entorhinal cortex [3–5]. Despite large research efforts to understand the mechanisms triggering β-amyloid accumulation in sporadic AD, the cause remains elusive.

Animal models have suggested a role for vascular pathology and cerebral hypoperfusion in the development of β-amyloid pathology [6–9]. A transient bilateral occlusion of the common carotid arteries in rats induces a nuclear translocation of HIF1α (hypoxia inducible factor1α), thereby increasing the expression of the β-secretase 1 enzyme. β-secretase 1 in turn increases the conversion of the amyloid precursor protein to β-amyloid$_{1–42}$ [6,10]. In humans, there is a clear reduction of cerebral perfusion in affected regions in patients with manifest AD and mild cognitive impairment due to AD [11–13]. Moreover, postmortem tissue from AD patients shows evidence of hypoxia-induced alterations in protein expression in areas with β-amyloid pathology [14,15]. These findings has led to the hypothesis that vascular pathology and hypoperfusion

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might precede β-amyloid accumulation in AD [9,16,17], but whether they actually represent a cause or a downstream effect is not known, and data from human subjects are lacking.

To examine whether cerebral hypoperfusion increases β-amyloid deposition in humans, we studied a group of patients ($n = 11$) with longstanding unilateral internal carotid artery (ICA) occlusion or middle cerebral artery (MCA) stenosis, resulting in uneven perfusion of the cerebral hemispheres. We hypothesized that the hypoperfusion would lead to a unilateral increased deposition of β-amyloid fibrils as visualized with β-amyloid positron emission tomography (PET) imaging. A subset of patients also underwent ^{18}F-AV-1451 PET scans.

2. Methods

2.1. Participants with unilateral ICA occlusion or MCA stenosis

Patients with a diagnosis of stenosis or occlusion of precerebral arteries, seen at the Department of Neurology, Skåne University Hospital, Sweden, January 2012–May 2014, were assessed for participation in the study. Inclusion criteria were occlusion or near-occlusion (noncontinuous blood flow) of one of the ICA or a significant stenosis of one of the MCA resulting in a unilateral decrease in cerebral perfusion. Exclusion criteria were major psychiatric disease, neurological disease other than transient ischemic attack or stroke, major stroke in the affected hemisphere, and dementia or major somatic illness. Nineteen patients met the inclusion criteria and were asked to participate in the study. Twelve patients agreed to participate, and eleven patients completed the study. All patients received oral and written information about the study and signed an informed consent form before being enrolled. All procedures were conforming to the Declaration of Helsinki and were reviewed and approved by the regional Ethical Committee at Lund University and the Radiation Protection Committee at Skåne University Hospital.

Patients underwent neurological and clinical examination, assessment of previous and concomitant diseases, and medication. Patients were tested at the baseline visit using Mini-Mental State Examination and Hospital Anxiety and Depression Scale [18,19]. Neuropsychological testing was performed at a separate visit and included the Boston Naming Test [20] (verbal naming), Rey Auditory Verbal Learning Test [21] (verbal memory), Brief-Visuospatial Memory Test-Revised [22] (spatial memory), Digit span from the Wechsler Adult Intelligence Scale-IV (working memory/attention), Verbal fluency from the Delis-Kaplan Executive Function System (verbal/mental speed), and Trail making test from the Delis-Kaplan Executive Function System (psychomotor speed/simultaneous attention).

2.2. Image acquisition

2.2.1. Magnetic resonance imaging/computed tomography

The patients underwent an extended magnetic resonance imaging (MRI) scan on a 3T scanner (Siemens Skyra, Munich, Germany), comprising contrast-enhanced MR angiography and T2*-weighted MR perfusion as well as high-resolution T1 (magnetization-prepared rapid gradient echo) and fluid-attenuated inversion recovery sequences. Sequence details are provided in the supplementary information (Supplementary Material). Due to contraindications to MRI, two patients underwent plain-computed tomography (CT), CT angiography, and CT perfusion on a Philips Brilliance 64 CT scanner (Philips, Best, the Netherlands) according to routine clinical protocols. In one patient, with reduced renal function, ICA occlusion was verified using Doppler ultrasonography on a Philips iU22 ultrasound system.

2.2.2. PET

^{18}F-Flutemetamol was obtained from General Electric (GE, Risø, Denmark), and the scanning procedures have been described previously [23]. In brief, the patients received 196 ± 2 MBq ^{18}F-Flutemetamol via an intravenous injection in the antecubital vein. On a separate day, a subset ($n = 5$) of the patients received an average of 372 ± 2 MBq ^{18}F-AV-1451. The radiosynthesis of AV-1451 has been described previously [24]. The PET data were acquired on a Philips Gemini TF PET-CT scanner as 4 × 5 minute dynamic time frames, 80–100 minutes postinjection.

2.2.3. Image analysis

Maps of the mean transit time (MTT) and relative cerebral blood flow (rCBF) were calculated from MR data using nordicICE (NordicNeuroLab, Bergen, Norway) and from CT data using software provided by the manufacturer. The presence of infarctions and the degree of stenosis or occlusion in the cervical and cerebral arteries were assessed.

PET data analysis was performed using Pmod 3.603 (Pmod technologies, Zurich, Switzerland). PET images were imported along with high-resolution T1, rCBF, and MTT images. T1 images were segmented into gray and white matter and coregistered to the PET data using the NeuroTool. The brains were segmented using the Automated Anatomical Labeling-atlas, and the cerebellar gray matter regions excluding the vermis were pooled into a composite reference region. Using rCBF, MTT, and magnetization-prepared rapid gradient echo images, areas with hypoperfusion without visible cerebral infarctions on structural sequences were identified. In the area with the most pronounced perfusion changes, one 15-mm diameter spherical hypoperfused volume of interest (VOI) per subject was created. The hypoperfused VOI was then mirrored onto the contralateral (control) hemisphere and intersected using the gray/white matter segmentation mask into VOIs consisting of hypoperfused and more normally perfused cortex and white matter. VOIs were created in the MRI images by a person blinded to the PET data. The rCBF and MTT maps from MRI and PET images were coregistered to the T1 using the Fusion tool. The VOIs were then used for measuring average rCBF and MTT values as well as ^{18}F-Flutemetamol and