Cerebral hypoperfusion is not associated with an increase in amyloid β 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 amyloid β (\textsuperscript{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 (\textsuperscript{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 \textsuperscript{18}F-Flutemetamol or \textsuperscript{18}F-AV-1451 was not altered.

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

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

1. Introduction

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 amyloid β (Aβ) plaques and tau-containing neurofibrillary tangles [2]. Aβ accumulation is believed to be the crucial mechanism in AD, starting decades before clinical symptoms, and the presence of Aβ 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 Aβ accumulation in sporadic AD, the cause remains elusive.

Animal models have suggested a role for vascular pathology and cerebral hypoperfusion in the development of Aβ pathology [6–9]. A transient bilateral occlusion of the common carotid arteries in rodents 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 Aβ\textsubscript{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 Aβ pathology [14,15].

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These findings have led to the hypothesis that vascular pathology and hypoperfusion might precede Aβ 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 Aβ 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 Aβ fibrils as visualized with Aβ positron emission tomography (PET) imaging. A subset of patients also underwent 18F-AV-1451 PET scans.

2. Methods

2.1. Participants

Patients with a diagnosis of stenosis or occlusion of cerebral 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

18F-Flutemetamol was obtained from General Electric (GE, Riso, Denmark), and the scanning procedures have been described previously [23]. In brief, the patients received 196 ± 2 MBq 18F-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 18F-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 18F-Flutemetamol and...
18F-AV-1451 standardized uptake value ratios (SUVRs). SUVR values were calculated using cerebellar composite gray matter as the reference region. In the two cases where an MRI scan was missing, the VOIs were delineated on a CT scan fused to the PET image, and areas of hypoperfusion were assessed using data from CT perfusion maps. 18F-Flutemetamol uptake in the brain was also measured in a neocortical composite VOI [23] using NeuroMarq (GE Healthcare) to determine amyloid positivity. A previously established cutoff of >1.42 SUVR was used for abnormal Aβ uptake [23]. As an additional measure, a larger composite region was created in medial cerebral artery–perfused territory (described in detail the supplementary methods [Supplementary Material]).

2.2.4. Statistics
Statistical analyses were performed using GraphPad Prism 7 for Macintosh or IBM SPSS Statistics for Macintosh, version 23. For assessing differences between hypoperfused and contralateral normally perfused areas, Wilcoxon’s signed-rank test was used. Correlations were assessed using Spearman correlations. Statistical significance was considered being P < .05.

3. Results
3.1. Participants
The clinical characteristics of the study participants are described in Table 1. All 11 subjects were nondemented and had a median age of 69 years (range 51–83 years). They had a unilateral near-occlusion or occlusion in the ICA or a significant unilateral stenosis in the MCA resulting in a regionally reduced cerebral perfusion. The median time of known artery occlusion was 22 months (range 9–258 months) (Table 1). The pathogenesis for arterial occlusion was atherosclerotic disease in all but one, who received radiation therapy against a tonsillary adenocarcinoma a decade before enrollment in this study. The blood flow in the analyzed hypoperfused regions was 84% (interquartile range [IQR], 66–90; P < .01) of the blood flow in the contralateral side of the brain. The median MTT was 135% (IQR 115–202; P < .01) of the time in the contralateral side.

3.2. Amyloid and tau deposition
To study whether the reduced blood flow would result in deposition of Aβ or tau, we assessed the retention of 18F-Flutemetamol in all participants (n = 11) and of 18F-AV-1451 in a subset of subjects (n = 5).

We found no effect on regional amyloid or tau deposition in the hypoperfused versus more normally perfused regions in the brain. The median 18F-Flutemetamol SUVR was 1.35 (IQR 1.32–1.40) in the hypoperfused region versus 1.32 SUVR (IQR 1.28–1.46) in the normal region (P = .97; Fig. 1A). Similarly, the median 18F-AV-1451 SUVR was 1.09 (IQR 1.08–1.11) in the hypoperfused region versus 1.12 SUVR (IQR 1.09–1.13) in the normal region (P = .44; Fig. 1B). We also examined ratios of cortex/white matter retention in both hypoperfused and normal regions to account for the potential error introduced by a reduced perfusion leading to a reduced delivery of radiotracer to the hypoperfused regions and falsely low results in these regions. Using this approach, we again found no differences in amyloid or tau deposition (18F-Flutemetamol hypoperfused vs. normal: 0.68 [IQR 0.62–0.70] vs. 0.66 [0.63–0.70], P = .90; 18F-AV-1451 hypoperfused vs. normal: 0.91 [IQR 0.88–1.06] vs. 0.96 [IQR 0.91–1.06], P = .19; Fig. 1C and 1D). Two subjects had bilateral abnormal neocortical 18F-Flutemetamol uptake (composite score >1.42, Fig. 2D and Supplementary Fig. 1E), but no asymmetry was detected in these cases.

We next correlated the ratio of the 18F-Flutemetamol cortex/white matter (Wm) ratios (i.e., (Ctx Hypo/Wm Hypo)/(Ctx Normal/Wm Normal)) to the blood flow measurements (rCBF, MTT). We found no significant correlation between these two measures, again indicating that a more severe blood flow reduction is not coupled to increased Aβ deposition (Fig. 1E shows the rCBF data). Further, correlating the ratio above to time with arterial occlusion did not result in a significant correlation, indicating that an increased time with an arterial occlusion is not associated to an increased amyloid deposition in the affected areas (Fig. 1F). We further compared the 18F-Flutemetamol PET retention in the hypoperfused and contralateral cortex in composite regions supplied by the MCA. No changes in PET retention were seen between the hypoperfused and the normally perfused hemisphere in these larger regions (data not shown).

4. Discussion
Several studies have indicated that cerebral hypoperfusion increases amyloid deposition in animals [6–8,10], and vascular pathology has been proposed as an early causative event in the development of AD [9,16,17]. Using a multimodal imaging approach to assess the effects of cerebral hypoperfusion on Aβ deposition in the brain, we studied 11 patients with large vessel occlusion or stenosis resulting in a chronic unilateral hypoperfusion of the brain. We hypothesized that the brain regions with a reduction in cerebral perfusion would show an increased Aβ deposition. In contrast to our initial hypothesis, and to the results from animal studies [6,8], we found that hypoperfusion did not result in increased Aβ deposition compared with regions with a more normal perfusion. To account for the possibility that a decreased perfusion results in a reduced delivery of 18F-Flutemetamol, we compared ratios of cortex SUVRs divided by SUVRs in the underlying white matter with the assumption that white matter would be equally affected by a reduced delivery. The ratios again showed no difference between
| Case | Cerebral blood vessels | Perfusion decrease (MRI rCBF, %) | Time with occlusion (months) | Presenting symptom | Remaining symptoms | MMSE | Composite score (flutemetamol) (≥ −1.5 SD) | Neuropsychology |
|------|------------------------|----------------------------------|-----------------------------|-------------------|-------------------|------|------------------------------------------|----------------|
| Case 1 | Right >99% ICA stenosis. | 34 | 34 | TIA | None | 29 | 1.20 | Verbal memory |
| Case 2 | Right ICA occlusion. | 12 | 38 | Minor stroke (right occipital infarction) | None | 30 | 1.19 | No objective deficit |
| Case 3 | Right and left ICA occluded, vertebral arteries occluded. 50% stenosis of left MCA. Cerebral perfusion via collaterals from thyrocervical, ECA and optic arteries. | N/A | 24 | Dysfasia, infarction in left basal ganglia. | Discrete weakness in right arm and leg. | 28 | 1.16 | No objective deficit |
| Case 4 | Right ICA occlusion. Left 80% ICA stenosis. | 42 | 14 | TIA, left sided weakness | Discrete weakness of left hand. | 29 | 1.25 | Verbal and spatial memory |
| Case 5 | Left ICA occlusion | 34 | 28 | Accidental finding | None | 27 | 1.06 | Attention |
| Case 6 | Left ICA occlusion. Right 70% stenosis | 11 | 14 | Occipital infarction due to atrial fibrillation | Right homonymous upper quadrant anopsia | 30 | 1.18 | Spatial memory |
| Case 7 | Right ICA occlusion. Left 90% stenosis | 16 | 22 | TIA, left sided weakness | None | 28 | 2.23 | Verbal and spatial memory |
| Case 8 | Right ICA occlusion | 19 | 10 | Minor stroke. Left sided weakness | None | 29 | 1.34 | Executive function |
| Case 9 | Left ICA occlusion | 9 | 9 | Minor stroke. Weakness right hand | None | 30 | 1.36 | No objective deficit |
| Case 10 | Left ICA occlusion | N/A | 35 | Minor stroke. | None | 30 | 1.48 | N/A |
| Case 11 | Left ICA occlusion | 7 | 258 | Unknown | None | 29 | 1.22 | No objective deficit |

Abbreviations: MRI, magnetic resonance imaging; rCBF, relative cerebral blood flow; MMSE, Mini-Mental State Examination; TIA, transient ischemic attack; ICA, internal carotid artery; MCA, middle cerebral artery; ECA, external carotid artery; N/A, not available.
hypoperfused and control regions. Nor did we find any differences in AV-1451 uptake indicating no effect of hypoperfusion on tau deposition. We further correlated the $^{18}$F-Flutemetamol SUVRs to time with cerebral hypoperfusion or to the degree of hypoperfusion but found no effect of these measures on Aβ deposition.

Alterations in cerebral blood flow autoregulation [25] and reduction in cerebral blood flow have been detected in patients with advanced heart failure [26]. In line with the data presented here, a recent large Danish epidemiological study of 324,000 patients with heart failure and 1.6 million controls did not find an increased risk of developing AD in patients with heart failure, in sharp contrast to a clearly increased risk of developing vascular dementia [27]. As a supplemental analysis, we therefore studied amyloid PET positivity in patients with orthostatic hypotension compared with nonorthostatic patients in a separate cohort (the BioFINDER cohort, $n = 361$ nondemented participants) but found no differences between the groups (see Supplementary Material for details).

Fig. 1. Aβ and tau retention. SUVR values of (A) $^{18}$F-Flutemetamol and (B) $^{18}$F-AV-1451 in the hypoperfused cortex (CtxHypo) and contralateral cortex (CtxCtrl). The cortex/white matter ratio of (C) $^{18}$F-Flutemetamol and (D) $^{18}$F-AV-1451 in the hypoperfused (CtxH/WmH) and contralateral (CtxC/WmC) regions. (E) Relative blood flow (rCBF) (hypoperfused side/contralateral side) plotted against a ratio of the cortex/white matter ratios of $^{18}$F-Flutemetamol retention $(\text{CtxH/WmH})/(\text{CtxC/WmC})$. (F) The $^{18}$F-Flutemetamol ratio plotted against time with verified occlusion in months. Note that there is a gap in the x-axis.

Abbreviations: SUVR, standardized uptake value ratio; Ctx, cerebral cortex; Wm, cerebral white matter.
It could be argued that the patients included in the study are too young to develop Aβ aggregation (median age 69 years). However, at this age, Aβ aggregation is getting increasingly more common and is present in approximately 20% of controls of similar age in our parallel BioFINDER study. We believe that if the subjects enrolled in the study would have had an increased propensity to aggregate Aβ, we should have detected this. Further, in the two cases with abnormal 18F-Flutemetamol retention in the study, no asymmetry was detected. It could also be argued that the time with hypoperfusion is not enough for accumulation of Aβ. Animal data however seem to indicate rapid changes in response to hypoperfusion [6], and one of the participants in this study had had an occlusion for more than 20 years without evidence of increased Aβ accumulation. Moreover, the subject with the highest SUVRs for 18F-Flutemetamol was diagnosed with an occlusion 22 months before the time of the 18F-Flutemetamol PET scan. This subject had an 85% stenosis already, 15 years before the diagnosis of an occlusion, and has thus been accumulating Aβ, resulting in an abnormal amyloid PET, but without evidence of increased aggregation in the hypoperfused parts of the brain.

Our results indicate that cerebral hypoperfusion caused by large vessel occlusion due to arteriosclerosis does not induce accumulation of Aβ. However, this does not entirely exclude the possibility that an altered blood flow supply of nutrients due to pathology in small-vessel disease may affect

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**Fig. 2.** Multimodal imaging of all study subjects with a complete set of AV-1451 PET, Flutemetamol PET, and MRI (n = 5). Presented are transversal images of T1-MPRAGE, mean transit time (MTT), relative cerebral blood flow (rCBF), 18F-Flutemetamol PET SUVR, and 18F-AV-1451 PET SUVR images of cases: 1 (A), 2 (B), 5 (C), 7 (D), and 8 (E). The stars indicate the side affected by hypoperfusion. Circles indicate the locations of regional analysis in each patient. Arrows indicate an area with AV-1451 retention related to a cerebral infarction. Abbreviations: MRI, magnetic resonance imaging; SUVR, standardized uptake value ratio.
Using 18F-Flutemetamol we can not exclude the possibility that there may be an increase in the levels of soluble Aβ in the hypoperfused regions. Although we do not find any evidence that cerebral hypoperfusion caused by large vessel disease increases Aβ deposition, it is important to treat cardiovascular risk factors in the elderly population to lower the risk of vascular dementia and to reduce the additive effects of small-vessel pathology in AD.

In summary, we find that longstanding cerebral hypoperfusion due to large vessel disease in humans does not result in accumulation of Aβ fibrils or tau aggregates. This strongly indicates that the hypoperfusion detected in AD or in mild cognitive impairment due to AD is not a causative event in the pathophysiological mechanisms of the disease, but rather a reactive change due to decreased metabolic demand of affected parts of the brain.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2017.06.2265.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature using PubMed. Several articles have described an association between cerebral hypoperfusion and Aβ deposition in experimental models of Alzheimer’s disease. No conclusive evidence for a causal relationship in humans has been published. Relevant citations are appropriately cited.

2. Interpretation: Our findings show that longstanding cerebral hypoperfusion caused by unilateral precerebral large vessel occlusion does not affect amyloid or tau deposition in nondemented human subjects.

3. Future directions: This article provides the first evidence in man that cerebral hypoperfusion due to large vessel disease does not have a causative role in Alzheimer’s disease. Further studies are needed to address whether small-vessel disease, as, for example, caused by hypertension, is related to amyloid deposition.

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