Chronic hypoperfusion due to intracranial large artery stenosis is not associated with cerebral β-amyloid deposition and brain atrophy

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Abstract

Background: Insufficient cerebral perfusion is suggested to play a role in the development of Alzheimer disease (AD). However, there is a lack of direct evidence indicating whether hypoperfusion causes or aggravates AD pathology. We investigated the effect of chronic cerebral hypoperfusion on AD-related pathology in humans.

Methods: We enrolled a group of cognitively normal patients (median age: 64 years) with unilateral chronic cerebral hypoperfusion. Regions of interest with the most pronounced hypoperfusion changes were chosen in the hypoperfused region and were then mirrored in the contralateral hemisphere to create a control region with normal perfusion. ^{11}C-Pittsburgh compound-positron emission tomography standard uptake ratios and brain atrophy indices were calculated from the computed tomography images of each patient.

Results: The median age of the 10 participants, consisting of 4 males and 6 females, was 64 years (47–76 years). We found that there were no differences in standard uptake ratios of the cortex (volume of interest [VOI]: $P = 0.721$, region of interest [ROI]: $P = 0.241$) and grey/white ratio (VOI: $P = 0.333$, ROI: $P = 0.445$) and brain atrophy indices (Bicaudate, Bifrontal, Evans, Cella, Cella media, and Ventricular index, $P > 0.05$) between the hypoperfused regions and contralateral normally perfused regions in patients with unilateral chronic cerebral hypoperfusion.

Conclusion: Our findings suggest that chronic hypoperfusion due to large vessel stenosis may not directly induce cerebral β-amyloid deposition and neurodegeneration in humans.

Keywords: Cerebral hypoperfusion; β-amyloid; Brain atrophy; Alzheimer disease

Introduction

Alzheimer disease (AD) is the most common form of aging-related dementia, and it places a heavy burden on patients and society.[1] β-amyloid (Aβ) deposition is considered to be the key event in AD pathogenesis. However, the causes of AD remain unclear.[2]

There is a significant decrease in cerebral blood flow (CBF) and insufficient perfusion in the brains of AD patients.[3] A lack of perfusion has already occurred in the brains of mild cognitive impairment (MCI) patients[4,5]; the lack of perfusion is related to the rate of cognitive decline. A recent study involving the Alzheimer Disease Neuroimaging Initiative database discovered that in the progression from a healthy state to AD, insufficient cerebral perfusion may play an important role in initiating AD.[6] In addition, vascular risk factors (VRFs), such as hypertension, diabetes mellitus, cardiovascular diseases, and hypercholesterolemia, are associated with an increased risk of AD, exacerbation of cognitive decline and neurodegeneration, and amyloid deposition, which is presumed to be caused by chronic cerebral hypoperfusion,[7-9] supporting the causative roles of chronic cerebral hypoperfusion in the development of AD.

However, although chronic cerebral hypoperfusion modeled with surgical ligation of bilateral or unilateral

common carotid arteries increased Aβ deposition and neurodegeneration in AD animals,[10,11] no correlation between local amyloid deposition and local cerebral hypoperfusion was observed in humans.[12-14] In this study, we investigated the impact of chronic cerebral hypoperfusion on amyloid deposition and neurodegenerative changes in a group of cognitively normal patients with chronic unilateral cerebral hypoperfusion.

Methods

Ethical approval

This study was approved by the Institutional Review Board of Daping Hospital (2016-10) and conducted in accordance with the *Declaration of Helsinki*. Informed consents were obtained from participants or their guardians.

Study subjects

Patients with chronic unilateral cerebral hypoperfusion were recruited from the Registry of Neurodegeneration of Daping Hospital from January 2016 to December 2019. Chronic unilateral cerebral hypoperfusion was defined as the reduced perfusion in one cerebral hemisphere detected by computed tomography perfusion (CTP) with or without severe middle cerebral artery (MCA)/internal carotid artery (ICA) stenosis; the contralateral cerebral hemisphere of the same patient was set as the control. The subjects were not eligible if they had (1) cognitive decline caused by neurological diseases (*eg*, AD, MCI, vascular dementia, and Parkinson disease dementia); (2) a history of stroke, intracranial infection, or brain trauma; (3) heart disease (severe coronary heart disease, cardiac insufficiency, atrial fibrillation, *etc*); (4) severe liver, renal and pulmonary insufficiency; (5) concomitant disorders including hematological diseases, peptic ulcer, mental illness or epilepsy; or (6) an allergy to the ^{11}C-Pittsburgh compound.

Clinical assessments

Demographic characteristics, including age, sex, and education levels, were recorded. All subjects underwent clinical assessments, including medical history, physical examination, laboratory tests, apolipoprotein E genotyping, and neuropsychological tests. Computed tomography (CT), CT angiography (CTA), CTP, and ^{11}C-Pittsburgh compound-positron emission tomography (PiB-PET) examinations were performed. The Mini-Mental State Examination and Clinical Dementia Rating were administered to screen and assess overall cognitive function.[15]

Neuroimaging

Non-enhanced CT (NECT)/CTP/CTA acquisition

NECT/CTP/CTA was sequentially performed on a 256-slice multidetector CT scanner (Brilliance iCT, Philips Healthcare, Amsterdam, Netherlands). The parameters were as following. NECT: slice thickness = 5 mm, interlayer spacing = 5 mm, 120 kV, 150 mAs; CTP: 16 cm coverage in the z-axis, 80 kV, and 100 mA. The total acquisition time was 60 seconds (30 consecutive spiral acquisitions that were 2 seconds each). A total of 50 mL of contrast agent (Iopromide, Ultravist-370, Bayer Schering Pharma, Berlin, Germany) was injected intravenously followed by a 50-mL saline flush at 6.5 mL/s. CTA: coverage from vertex to aortic arch, slice thickness = 0.625 mm, interlayer spacing = 0.625 mm, 100 kV, and 150 mAs. A total of 50 mL of contrast agent (Iopromide, Ultravist-370, Bayer Schering Pharma) was injected intravenously followed by a 50-mL saline flush at 5.0 mL/s.

CTP data were processed using a post-processing station (IntelliSpace Portal, Philips, Amsterdam, Netherlands). The arterial input function was detected manually on the anterior cerebral artery to generate perfusion parametric maps for metrics including CBF, cerebral blood volume, mean transit time, and time to peak.

PET acquisition

All subjects were required to fast for at least 6 hours but had free access to water before the PET scan. PET scans were performed with a Siemens Biograph 64 PET/CT machine (Siemens, Munich, Germany) in three-dimensional mode. PiB-PET was performed according to standardized research protocols.[16] A dynamic 90-minute emission scan was administered with an intravenous injection of ^{11}C-PiB after 10 minutes of transmission scanning. Standardized images were extracted within the regulated interval time after injection. All scans were performed in a dimly lit and quiet room with subjects in a resting state.

Image analysis

Aβ burden

CapAIBL (Australian eHealth Research Centre, CSIRO, Australia) was used to calculate the cortical standard uptake ratios (SUVRs)[17] and determine the negative or positive PiB-PET amyloid burden using the cutoff value of 1.42.[18] Pmod software (version 3.5, Pmod Technologies, Zurich, Switzerland) was used to analyze the amyloid burden in the volume of interest (VOI) and region of interest (ROI). PiB-PET series and standard magnetic resonance imaging-T1 templates were spatially merged by the fusion module. VOIs and ROIs were delineated by a researcher in the magnetic resonance imaging according to the mean transit time and CBF of the CTP; the researcher was blinded to the PET images. A sphere (VOI) with a diameter of 15 mm was created in the region with the most pronounced hypoperfusion changes of each subject, and an irregular ROI was manually drawn to cover the hypoperfused region as much as possible. The hyperfused VOI and ROI were then mirrored in the contralateral hemisphere to create a control region (Ctrl) with normal perfusion. For 3 cases with minor infarcts, the infarction regions were completely avoided in the VOI and ROI.

All regions were then intersected using the grey/white matter (GM/WM) segmentation mask into VOIs (or ROIs) and controls. The SUVR of the cortex and WM in each region was subsequently measured using the cerebellar composite GM as the reference region.

Brain atrophy

In all patients, brain atrophy indices were measured on CT scans based on the commonly used method described by Meese *et al*[19]. These indices, including the bicaudate index, bifrontal index, Evans index, Cella index, Cella media index, and ventricular index, were calculated unilaterally by the distance from the midline of the brain (shown in detail in Figure 1B).[20,21] Every index was measured twice, and the mean value was calculated by RadiAnt DICOM Viewer 5.0.1 (Medixant, Poznan, Poland); this procedure was performed to increase accuracy and limit the "partial volume" effect.

Statistics analyses

Shapiro–Wilk test was used to test for a normal distribution. The differences in SUVRs and atrophy indices of bilateral cerebral hemispheres between the hypoperfused regions (Hypo) and the normally perfused Ctrl were analyzed using paired t tests. All hypothesis testing was two-sided, and statistical significance was defined as $P < 0.05$. All statistical computations were performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA).

Results

Characteristics of the study subjects

Subjects' characteristics are shown in Table 1. Fourteen patients met the inclusion criteria, 11 patients agreed to participate, and 10 of them completed the study. The median age of the 10 participants, consisting of 4 males and 6 females, was 64 years (47–76 years). All participants met the criteria for extensive CTP decline in the unilateral hemisphere without clinical manifestations of acute stroke or cognitive impairment. Six patients had occlusions in the ICA or MCA, 3 patients had severe stenosis of the ICA or MCA, and 1 patient had left frontal patchy hypoperfusion without obvious large vessel stenosis.

Hypoperfusion and Aβ burden

In all subjects, there was no significant difference in Aβ deposition between the hypoperfused regions (represented by VOIs and ROIs) and the normally perfused contralateral regions. In the spherical VOI where hypoperfusion was most pronounced, the median cortical SUVR was similar to that in the contralateral regions (1.11 [interquartile range {IQR} 1.02–1.11] *vs.* 1.10 [IQR 1.02–1.13], $P = 0.721$). In the ROI covering as much of the hypoperfused region as possible, the median cortical SUVR (1.11 [IQR 1.09–1.12]) was similar to that in the contralateral regions (1.10 [IQR 1.09–1.13]) ($P = 0.241$) (Figure 2A). Of note, one subject had bilateral abnormal ^{11}C-PiB uptake (composite score SUVR >1.42; Figure 3D).

There is a possibility that the cortical SUVR in the hypoperfused regions might have been underestimated due to the lower delivery of radiotracers to these regions. To correct the possible tracer entry error due to hypoperfusion, we evaluated the GM/WM retention ratio and found that there were no significant differences in VOIs (Hypo *vs.* Ctrl, 0.77 [IQR 0.71–0.87] *vs.* 0.78 [IQR 0.76–0.87], $P = 0.333$) or ROIs (Hypo *vs.* Ctrl, 0.84 [IQR 0.84–0.85] *vs.* 0.84 [IQR 0.84–0.85], $P = 0.445$) (Figure 2B) between the hypoperfused and contralateral regions.

Hypoperfusion and neurodegeneration

The neurodegeneration indicated by brain atrophy was further evaluated. In the 10 subjects, there were no significant differences between the Hypos and Ctrls in
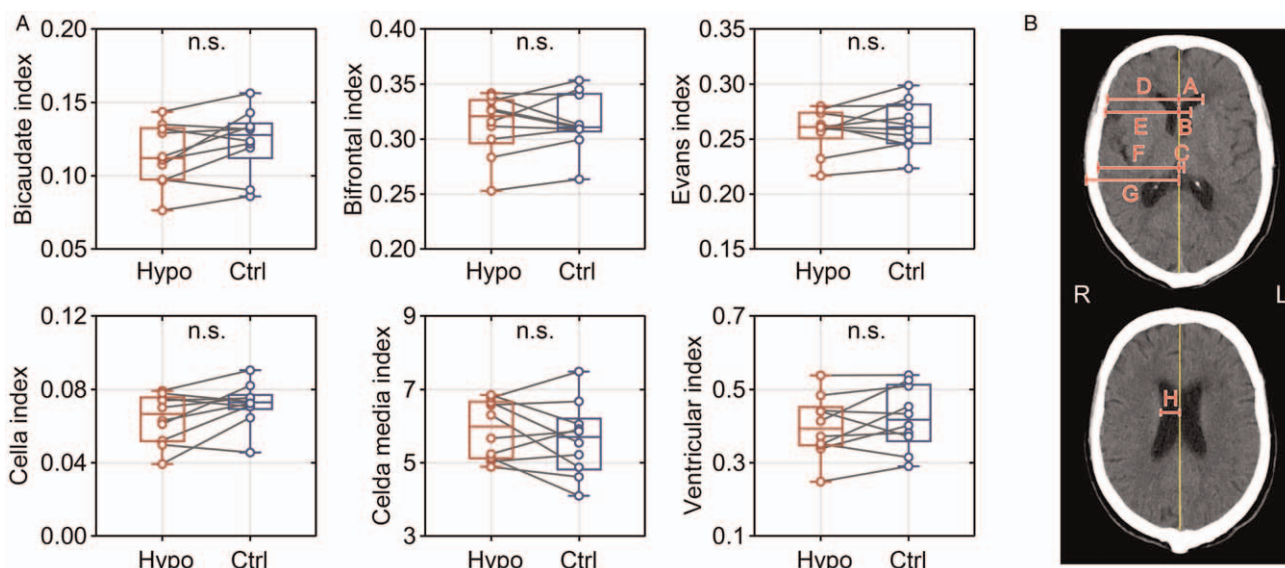

Figure 1: Hypoperfusion and brain atrophy. Brain atrophy indices of the bilateral hemisphere (A). CT indices used in this study (B). Bicaudate index = minimum width of the lateral ventricles/skull width at the same level = B/E. Bifrontal index = maximum width of the frontal horns/skull width at the same level = A/D. Evans index = maximum width of the frontal horns/skull width at the level of the third ventricle = A/F. Cella index = width of the third ventricle/skull width at the same level = C/F. Cella media index = maximum width of the skull/width of the lateral ventricles = G/H. Ventricular index = minimum width of the lateral ventricles/maximum width of frontal horns = B/A. $n = 10$. Hypo: Hypoperfused hemisphere; Ctrl: Contralateral hemisphere; CT: computed tomography; n.s. denotes no statistical difference.

Table 1: Characteristics of the patients with chronic unilateral cerebral hypoperfusion.

Case No.	Age (yrs)	Sex	APOE ε4 genotype	Vessels responsible for hypoperfusion	Diagnosis	SUVRs	MMSE (Education level)	CDR
1	68	Female	ε2/ε3	Right ICA stenosis (60%)	TIA	1.09	26 (6)	0
2	76	Male	ε3/ε3	Left frontal patchy hypoperfusion without obvious large vessel stenosis	TIA	1.07	29 (12)	0
3	55	Female	ε3/ε3	Left MCA occlusion	TIA	1.09	28 (12)	0
4	65	Male	ε3/ε4	Left ICA occlusion	Asymptomatic infarction (left frontal and parietal lobe)	1.63	26 (6)	0
5	60	Male	ε3/ε3	Right MCA severe stenosis (90%)	TIA	1.01	29 (6)	0
6	47	Male	ε3/ε3	Left MCA occlusion	TIA	0.84	29 (9)	0
7	60	Female	ε3/ε3	Left ICA occlusion	TIA	0.91		0
8	75	Female	ε3/ε4	Right MCA severe stenosis (90%)	TIA, asymptomatic infarction (right temporal lobe)	1.17	27 (9)	0
9	64	Female	ε3/ε4	Left MCA occlusion	TIA	1.13	25 (0)	0
10	64	Female	ε3/ε3	Left MCA occlusion	TIA, asymptomatic infarction (left parietal and occipital lobe)	1.10	26 (9)	0

APOE: Apolipoprotein E; CDR: Clinical Dementia Rating; ICA: Internal carotid artery; MCA: Middle cerebral artery; MMSE: Mini-Mental State Examination; SUVRs: Standard uptake ratios; TIA: Transient ischemic attack.
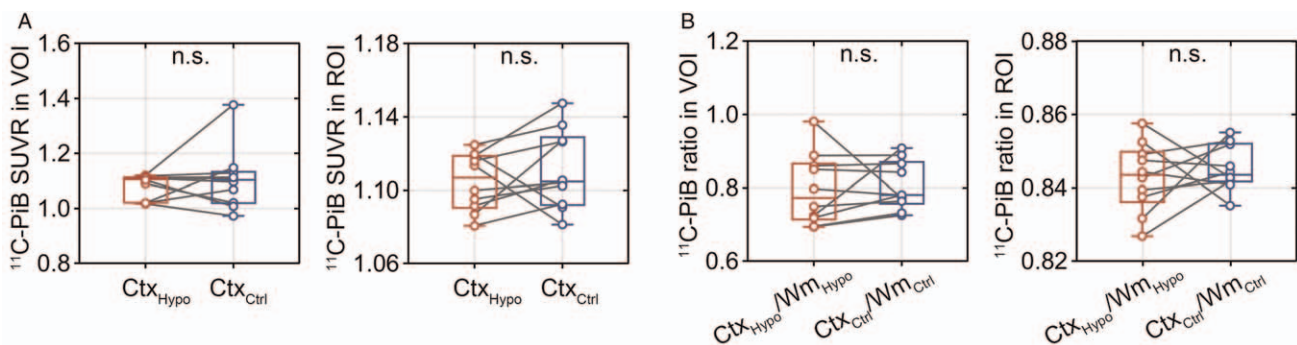

Figure 2: Hypoperfusion and Aβ burden. SUVRs of ^{11}C-PiB of the hypoperfused cortex (Ctx$_{Hypo}$) and normally perfused control cortex (Ctx$_{Ctrl}$) in the VOI and ROI (A). The cortex/white matter ratio of the hypoperfused region (Ctx$_{Hypo}$/Wm$_{Hypo}$) and normally perfused control cortex (Ctx$_{Ctrl}$/Wm$_{Ctrl}$) in the VOI and ROI (B). $n = 10$. Aβ: β-amyloid; Ctx: Cerebral cortex; Ctrl: Contralateral hemisphere; Hypo: Hypoperfused hemisphere; ROI: Region of interest; SUVRs: Standard uptake ratios; VOI: Volume of interest; Wm: Cerebral white matter; n.s. denotes no statistical difference.

brain atrophy indices, including the Bicaudate index (Hypo vs. Ctrl, 0.11 [IQR 0.10–0.13] vs. 0.13 [IQR 0.11–0.14], $P = 0.060$), Bifrontal index (Hypo vs. Ctrl, 0.32 [IQR 0.30–0.34] vs. 0.31 [IQR 0.31–0.34], $P = 0.707$), Evans index (Hypo vs. Ctrl, 0.26 [IQR 0.25–0.27] vs. 0.26 [IQR 0.25–0.28], $P = 0.384$), Cella index (Hypo vs. Ctrl, 0.07 [IQR 0.05–0.08] vs. 0.07 [IQR 0.07–0.08], $P = 0.051$), Cella media index (Hypo vs. Ctrl, 5.98 [IQR 5.11–6.68] vs. 5.70 [IQR 4.81–6.21], $P = 0.285$), and Ventricular index (Hypo vs. Ctrl, 0.39 [IQR 0.35–0.45] vs. 0.42 [IQR 0.36–0.51], $P = 0.216$) (Figure 1).

Discussion

VRFs are considered to increase the risk of AD and a decline in cognitive function; this may be caused by their effects on Aβ metabolism and neurodegeneration in the brain. A recent large prospective cohort study further focused on the relationship between VRFs and AD and found that midlife but not late-life VRFs were significantly associated with elevated amyloid deposition in cognitively normal participants.[22] This is probably due to insufficient cerebral blood supply, which may impair the function of the neurovascular unit, create an imbalance between the production and clearance of Aβ, and finally lead to the deterioration of pathological changes related to AD and cognitive dysfunction.[6,9] Indeed, cerebral hypoperfusion in the temporal and parietal lobes has been confirmed in AD patients.[3]

However, whether hypoperfusion can directly lead to AD-related pathological changes remains uncertain. Previous animal studies have found that cerebral hypoperfusion triggers Aβ deposition in the vessel wall parenchyma in the brain. In a mild chronic cerebral hypoperfusion animal model using C57BL/6J mice subjected to right common carotid artery permanent ligation, cerebral hypoperfusion triggered both early vascular deposition of peripherally applied human Aβ$_{42}$ peptides and small stable Aβ deposits in the hypoperfused brain parenchyma 6 weeks later.[11] In contrast, hypoperfusion was shown to have little or no effect on an altered brain Aβ burden in human studies,[12-14] which was consistent with the results of
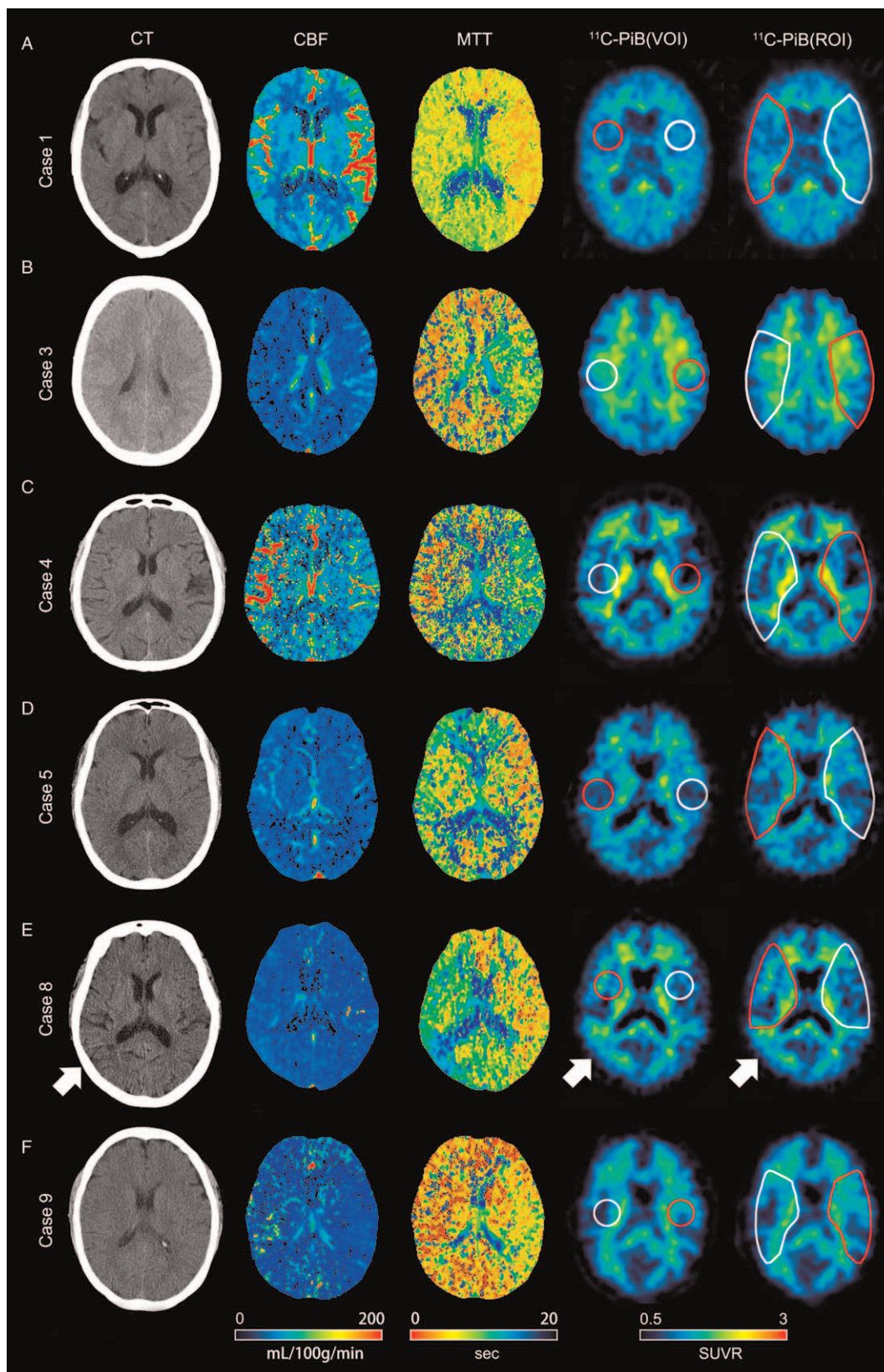
Figure 3: Representative multimodal imaging of six patients. Images of patients No. 1, 3, 4, 5, 8, and 9. (A–F) show the CT, CBF, MTT, ^{11}C-PiB-PET SUVRs in VOI, and ^{11}C-PiB-PET SUVRs in the ROI of each patient. Circles and irregular enclosed regions indicate the location of analysis; red represents the Hypo and white represents the normally perfused control region. Arrows indicate the corresponding area of the infarct in PiB-PET. CBF: Cerebral blood flow; CT: computed tomography; Hypo: Hypoperfused hemisphere; MTT: Mean transit time; PiB-PET: Pittsburgh compound-positron emission tomography; ROI: Region of interest; SUVRs: Standard uptake ratios; VOI: Volume of interest.

our study. As for hypoperfusion in an acute form, several studies found that acute ischemic stroke was not associated with sustained or increased Aβ deposition.[23,24] Therefore, it is indicated that neither chronic nor acute hypoperfusion has a direct impact on cerebral Aβ deposition.

Hypoperfusion was found to be associated with the progression from MCI to dementia and subsequent cognitive decline in humans.[25,26] However, it remains uncertain whether cerebral hypoperfusion can aggravate Aβ deposition and neurodegeneration in AD. In AD transgenic mice, ligation of carotid arteries increased Aβ deposition and neuron loss in the brain.[10,27] However, chronic cerebral hypoperfusion was not associated with increased Aβ deposition and aggravated brain atrophy in a pre-clinical AD subject who carried 1 apolipoprotein E ε4 allele and had obvious Aβ deposition in the brain in our study. To our knowledge, there is no direct evidence showing that cerebral hypoperfusion aggravates Aβ deposition in AD patients. This issue needs to be addressed in the future.

There were some strengths in our study. First, chronic hypoperfusion occurred on only one side in the included subjects, and the perfusion of the contralateral side was normal; thus, the influence of individual heterogeneity on the results could be eliminated. Second, major stroke patients were excluded due to the potential influence of infarction and the massive neuronal loss on Aβ deposition and neurodegeneration. Third, we enrolled relatively older patients with a median age of 64 years. These individuals were suitable for an examination of the impact of hypoperfusion on Aβ deposition and neurodegeneration as AD-related pathological changes are suggested to begin at 15–20 years before dementia onset.

The limitation of our study is that the sample size was relatively small, yet patients with chronic unilateral cerebral hypoperfusion were difficult to enroll in clinical practice. In addition, the duration of hypoperfusion of our participants was unknown. It cannot be excluded that the duration of hypoperfusion was not long enough to induce cerebral amyloidosis and neurodegeneration in our cohort. Small vessel diseases or microvascular changes in the brain may have an impact on the pathology of AD and may increase the risk of dementia.[28-30] However, our study only included patients with hypoperfusion due to intracranial large vessel stenosis but not small vessel diseases. It should be noted that the pathological changes in cerebral small vessels, such as WM hyperintensities and cerebral microbleeds, were not seen in our study subjects; besides, in the 3 subjects with lacunar infarcts, the VOIs and ROIs were carefully chosen to avoid the region of an infarct. Therefore, our results were unlikely to be confounded by small vessel lesions.

In conclusion, we found that chronic cerebral hypoperfusion due to large vessel stenosis is not associated with increased Aβ deposition or aggravated brain atrophy, implying that chronic hypoperfusion does not directly induce Aβ deposition and neurodegeneration in the brain.

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