Tau distribution in probable Cerebral Amyloid Angiopathy

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Abstract

Cerebrovascular deposition of amyloid-ß (cerebral amyloid angiopathy, CAA) is associated with magnetic resonance imaging findings of lobar hemorrhage, cerebral microbleeds, and~~or~~ cortical superficial siderosis. Although pathological studies suggest that ~~The aim was to evaluate the relationship between~~ tau may co-localise with vascular amyloid, with relevance for understanding disease mechanisms, this has not yet been investigated in CAA *in vivo*. ~~and tau in CAA patients.~~ We therefore used ~~Three patients with clinically diagnosed CAA underwent~~ [^{11}C]Pittsburgh Compound B PET or [18F] Florbetaben PET to measure amyloid burden, and [^{18}F]T807 to measure paired helical filament tau in patients with probable CAA. The regions with ~~that had~~ cerebral microbleeds or cortical superficial siderosis largely overlapped with those showing ~~regions that showed i~~increased [^{18}F]T807 and ~~uptake as well as~~ increased [^{11}C]PiB uptake. Our study ~~This~~ provides preliminary *in vivo* evidence that vascular amyloid is associated with local production of paired helical filament tau.

Introduction

Cerebral amyloid angiopathy (CAA) refers to a condition where ß-amyloid protein accumulates in the walls of small cortical and leptomeningeal arterioles and arteries~~es~~.[1-3] Although definite CAA can only be confirmed pathologically, the Boston ~~criteria are a set of~~ clinical radiological criteria allow the ~~to~~ diagnosis of~~e~~ CAA ~~in a~~ noninvasively with high specificity in patients with intracerebral haemorrahge ~~way~~(Knudsen paper ref). S~~Recent studies showed that s~~trictly lobar microbleeds or cortical superficial siderosis (cSS) are also a radiologic marker of CAA in populations without intracerebral hemorrhage.[4] Furthermore, ~~previous studies show that~~ cerebrovascular~~al~~ amyloid can be detected by amyloid imaging studies using PiB-PET.[5, 6]

Recent advances in in-vivo tau imaging have opened a new era in neurodegenerative disease research. The T807~~,~~ ~~one of the~~ tau tracer~~,~~ binds to paired helical filament ~~(PHF)~~ tau, and has provided valuable data on the distribution of tau in Alzheimer's disease ~~patients~~.[7-9] However, the ~~distribution of tau and the~~ relationship between vascular amyloid and tau in CAA patients has not been ~~are undd~~efined. Previous reports suggest that ~~have revealed that~~ abnormally phosphorylated tau accumulates around beta-amyloid laden arteries more than ~~exceeded that~~ around non-beta amyloid laden blood vessels.[10-12] We~~Therefore, we~~ tested the hypothesis that ~~zed that~~ CAA patients would have greater tau deposition in ~~the~~ regions of ~~where there is g~~greater vascular amyloid burden using ~~. Herein, we report 3 cases of clinically diagnosed CAA who underwent~~ [^{18}F]T807-PET and PiB-PET.~~.~~

Patients and Methods

Subjects

Among the patients who visited memory clinic at Samsung Medical Center, we recruited three patients who had strictly lobar MBs or cSS, indicating ~~which met cla inical~~ diagnosis of probable CAA according to the Boston~~'s~~ criteria (Table 1).[4, 13-15] All three patients underwent neuropsychological tests using a standardized neuropsychological battery,[16, 17] which showed that two patients (Case #1 and #2) had multiple domain amnestic MCI and one patient (Case #3) had amnestic~~-~~ type ~~of~~ dementia.

This study was approved by the Institutional Review Board of Samsung Medical Center. We obtained informed consent from all participants.

Assessment of cerebral microbleeds and cortical superficial siderosis on MRI

All the participants underwent brain MRI. T2, T2*, T1, FLAIR, and T2 Fast Field Echo (FFE) MR images were acquired at Samsung Medical Center using the same 3.0T MRI scanner (Philips 3.0T Achieva). Microbleeds were defined as homogenous round signal loss lesions (≤10mm in diameter) on T2*-weighted images.[18] Strictly lobar microbleeds were ~~was~~ defined as having microbleeds restricted ~~(~~exclusively~~)~~ to ~~a~~ lobar locations. Cortical superficial siderosis was also defined as linear hypointensities on T2*-weighted images consistent chronic blood residues in the superficial layers of the cerebral cortex.[19]

Amyloid PET acquisition and data analysis

Case #2 and #3 underwent [^{11}C]Pittsburg compound B (PiB) PET at Samsung Medical Center using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI, USA) in a 3-dimensional scanning mode that examined 35 slices of 4.25-mm thickness spanning the entire brain. [^{11}C]PiB was injected into an antecubital vein as a bolus injection with a mean dose of 420 MBq (i.e., range 259–550 MBq). 60 minutes after injection, a CT scan was performed for attenuation correction. A 30-minute emission static PET scan was

then initiated. Attenuation corrected PET images were reconstructed from the CT data using an iterative reconstruction method. The specific radioactivity of [^{11}C]PiB at the time of administration was higher than 33.3 GBq/μmol for patients. In all PET studies, the radiochemical purity of the radiotracer was higher than 95%.

Case #1 underwent [^{F}18] Florbetaben PET at Samsung Medical Center using XXX scanner. The images were acquired at 90 minutes after the intravenous bolus injection of 283.2 ± 31.3 MBq of 18F-florbetaben for 20 minutes.

T-807 PET acquisition and data analysis

All three patients underwent T807 PET at Gangnam Severance Hospital using a Biograph mCT PET/CT scanner (Siemens Medical Solutions; Malvern, PA, USA). We acquired amyloid and tau PET scans on separate days. Tau PET images were acquired for 20 minutes, starting at 80 minutes after the intravenous bolus injection of 275.2 ± 28.0 MBq of 18F-AV-1451. Prior to the PET scan, we applied a head holder to minimize head motion and also acquired brain computed tomography (CT) images for attenuation correction. Finally, using the ordered-subsets expectation maximization (OSEM) algorithm (iteration = 6 and subset =16), 3D PET images were reconstructed in a 256 × 256 × 223 matrix with a 1.591 ×1.591 × 1 mm voxel size.

Results

In all three patients, the regions with ~~that had~~ CMBs or cSS largely overlapped with regions that showed increased [18F] T807 retention. The first case showed multiple CMBs in the left parietal and temporal areas, which ~~and~~ largely overlap with T807 uptake (Figure 1).

Florbetaben PET was ~~revealed to be~~ negative by visual rating. The second case showed asymmetric multiple CMBs in the left temporal area, corresponding ~~which corresponds~~ to the area of high PiB uptake. Asymmetric high T807 uptake was observed in the inferior temporal area, paralleling the area of CMB or cSS identified by T2* weighted images (Figure 1). The third case showed asymmetric CMB or cSS in the right parietal, occipital, and temporal areas, also co-localising with ~~where~~ high PiB uptake was seen. Although high T807 uptake was observed in the bilateral parietal, occipital, and temporal areas, there was preferential uptake on the ~~asymmetry toward the~~ right side, where CMBs or cSS were identified.

Discussion~~s~~

We report the imaging findings of three patients ~~cases w~~with clinically probable CAA with ~~ho had asymmetric distribution of strictly~~ multiple lobar CMBs or cSS, indicating probable CAA: the first ~~case~~ had left hemispheric dominant distribution of CMB, while ~~and~~ the other two ~~second and third cases~~ had a posterior ~~dominant~~ distribution of CMBs. In each patient, ~~Their~~ [^{18}F] T-807 PET showed increased ~~T-807~~ uptake~~s~~ in regions ~~especially in neighboring regions~~ where CMB or cSS were located~~distributed~~, providing ~~the~~ preliminary *in vivo* evidence that vascular amyloid might be co-localised with ~~be associated with local production of~~ paired helical filament ~~PHF form of~~ tau.

Our finding ~~that clinical probable CAA had increased T-807 uptakes especially in the neighboring region where CMB or cSS were located~~ is consistent with ~~previous~~ immunohistochemical studies showing tau immunopositive neurites clustered around cortical arteries ~~with~~ affected by amyloid angiopathy,~~.~~[10, 11] suggesting that peri-vascular accumulation of hyperphosphorylated tau may result from elevated levels of soluble amyloid beta 1-40

around cortical arteries and arterioles (ref 10). However, a recent *in vitro* study found ~~showed that there was~~ no autoradiographic binding of T807 in CAA or cSS lesions, containing hemosiderin deposits.[20] This discrepancy might be related to differences in binding conditions (*in vivo* versus *in vitro* autoradiographic binding). Our hypothesis that lobar CMB or cSS (indicating CAA) are related to local accumulation or production of tau is supported by a CSF biomarker study showing that patients with clinically probable CAA had higher t-tau and p-tau compared to controls.[3] An alternative explanation is that~~Our suggestion that lobar CMB or cSS are related to local production of tau is supported by a CSF biomarker study showing that clinical probable CAA patients had higher t-tau and p-tau compared to controls.[3] It is possible that~~ T807 ~~may~~ binds to hemosiderin deposits in the local hemorrhagic lesions, a~~. A~~lthough the regions of increased T807 uptake~~s~~ did not exactly parallel ~~overlap with~~ the distribution of CMBs or cSS~~, they clearly showed tendency toward neighboring regions of CMB or cSS location~~. Finally, we cannot exclude the possibility that tau may exist in relation to rapidly progressive neurodegeneration, rather than being specifically related to CAA.[21-24]

We noted that ~~also found that~~ the distribution ~~s~~ of PiB uptake in Case 2 and 3 was ~~were~~ different from typical pattern of amyloid distribution in AD, but rather largely overlapped with CMB or cSS ~~lesions which were distributed~~ in ~~the~~ posterior brain regions. Our findings are thus ~~were~~ consistent with previous studies showing a greater occipital-to-global PiB ratio in probable CAA ~~subjects~~ compared to AD ~~subjects~~.[25, 26] By contrast, ~~However, interestingly,~~ there was no~~ere no~~ increase in florbetaben uptake~~s~~ in the left hemisphere of case 1, where there were many CMBs; this ~~. This~~ might be due to difference in the amyloid tracer, or less ~~. Alternatively, case 1 might not have~~ advanced ~~degree of~~ CAA than the ~~unlike~~ other cases. Indeed, a~~A~~ previous study showed that mild ~~degree of~~ CAA might not be associated with amyloid uptake~~s~~ detected by *in -vivo* PET (Seo et al., AAIC

2015). Further studies of amyloid PET imaging in various stages of CAA patients using different~~various~~ amyloid tracers are needed.

Our study has limitations: we did not have ~~The limitation of this study is lack of~~ pathological confirmation of CAA, and the use of ~~y data to confirm the clinical diagnosis and PET findings. In addition,~~ different amyloid tracers might have affected the ~~were used to in amyloid PET imaging which gave inconsistent results regarding~~ relationships between amyloid and tau/CMB. Nevertheless, our findings provide new *in vivo* evidence that ~~to our knowledge, this is the first study to evaluate T807 distribution in CAA patients. Our novel findings suggest that~~ vascular amyloid might be associated with local production of paired helical filament ~~PHF form of~~ tau.

Table 1 Characteristics of clinically diagnosed CAA patients

	Case #1	Case #2	Case #3
Age	74	85	70
Gender	F	M	F
Education	16 years	12 years	9 years
APOE genotype	e3/e4	e3/e4	e3/e4
MMSE	20	23	14
Lobar Microbleeds, n	82	14	5
cSS, n[DW1]	0	2	1
Lacunes, n	4	0	0
WMH*	moderate	moderate	moderate
Medial temporal atrophy**	G1/G3	G2/G2	G2/G1
Amyloid PET	[^{18}F]Florbetaben negative	[^{11}C]PiB positive	[^{11}C]PiB positive
Initial symptoms	Word finding difficulty Memory impairment	Word finding difficulty Memory impairment Visuospatial dysfunction Irritability	Word finding difficulty Memory impairment
Disease duration	5 years	6 years	5 years
Cognitive test result	Multiple domain amnestic MCI	Multiple domain amnestic MCI	Dementia
Neurological examination	Unremarkable	Unremarkable	Unremarkable

*mild: periventricular white matter hyperintensities (WMH) < 5mm and deep WMH < 10mm

Moderate: between mild and severe

Severe: periventricular WMH ≥ 5mm and deep WMH≥ 10mm

** graded by Schelten's criteria (REF)

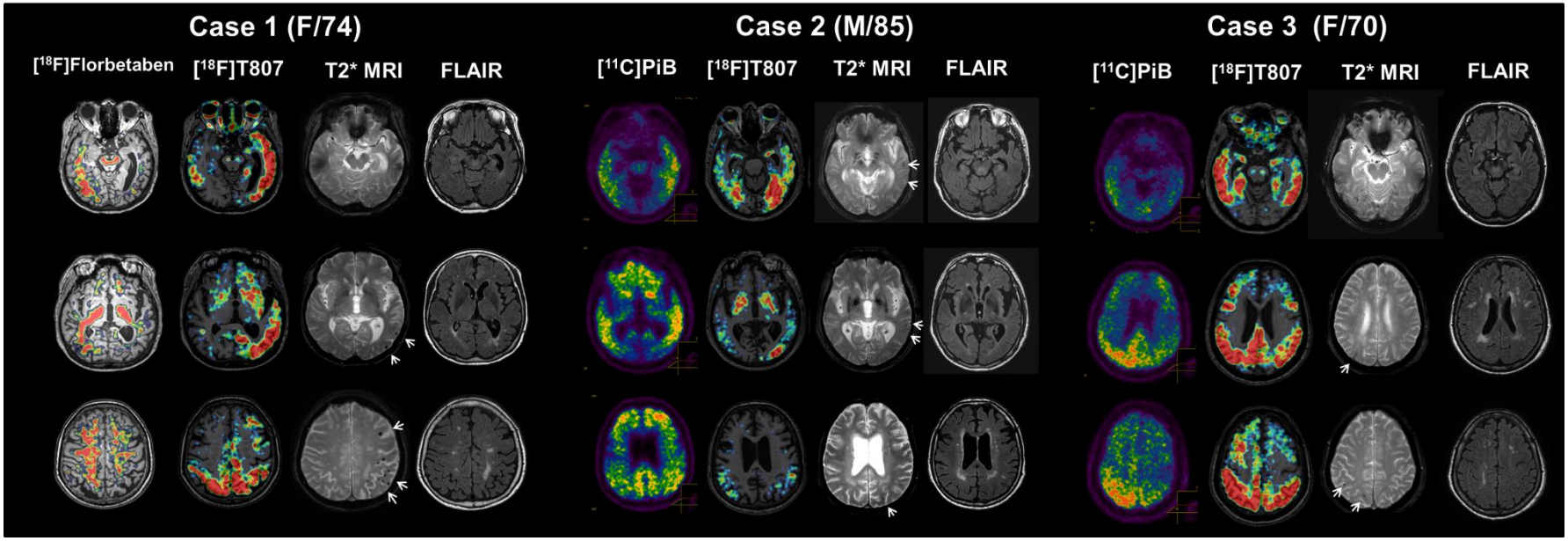

Figure legends

Figure 1. [18F]Florbetaben, [11C]Pittsburgh compound B (PiB), [18F]T807 PET, T2* weighted MRI, and FLAIR in probable CAA patients

Colored areas for [18F]Florbetaben or [18F]T807 PET represents SUVR ≥1.5 (ref: cerebellar gray matter).

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