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ASSOCIATION BETWEEN AMYLOID, TAU AND CEREBRAL SMALL VESSEL DISEASE

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Introduction

- According to 2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework ,AD refers to an aggregate of neuropathologic changes characteristic by 2 core pathologic molecular biomarkers, beta-amyloid (A+) and pathological tau (T+), which can be documented by CSF biomarkers or PET image *in vivo*.
- The subjects with A+T+, with or without neurodegeneration, are expected to have high rate of short-term clinical progression.[1]
- Cerebral small vessel disease (CSVD) is a group of pathological processes involved into the small arteries, and capillaries of the brain, MRI features including lacunes, white matter hyperintensities(WMH), perivascular spaces, microbleeds.[2]
- Mixed β-amyloid deposition/pathologic tau and CSVD pathology is commonly seen in patients with clinically diagnosed AD in autopsy, and the co-occurrence increases the risk of dementia.[3]
- Controversy exists with respect to the etiological role of cerebral small vessel disease (CSVD) in Alzheimer's disease (AD). We thus evaluated the association between white matter hyperintensity (WMH), an MRI marker of CSVD, with brain amyloid β (Aβ) and tau burden and their plasma markers among subjects with varying severity levels of cognitive impairment.

Methods and Materials

Participants of this study were recruited from an on-going CU-SEEDS (The Chinese University of Hong Kong – Screening for Early AlzhEimer's DiseaSe) study.

- Syndromal staging of cognitive continuum were classified as healthy controls (HC), subjective cognitive decline (SCD), mild cognitive impairment (MCI), dementia, by Chinese Abbreviated Memory Inventory (CAMI), Hong Kong List Learning Test (HKLLT) and Hong Kong version of Montreal Cognitive Assessment (HK-MoCA).
- 11C- PIB and 18F-T807 PET/CT to quantify Aβ and tau deposition
- Defined A+ if increased 11C-PIB uptake was visually observed in regions known to have beta-amyloid deposits in patients with AD dementia, and/or global retention ≥1.42. T+ if increased 18F-T807 uptake was visually observed in regions known to have tau deposits in AD ,and/or (2) SUVR ≥1.14.
- Structural MRI was performed on 3.0 Tesla scanner (Achieva TX; Philips Medical Systems, Best, Netherlands).
- Total intracranial volume and WMH volume were quantified automatically by AccuBrain® IV 1.1 (BrainNow Medical Technology Company Ltd.)
- Plasma levels of Aβ40, Aβ42, total tau (t-tau), phosphorylated tau at 181 (p-tau181) and neurofilament light chain (NfL) (SiMoA)

Results

A total of 84 stroke-free subjects (healthy controls (HC)=10; subjective cognitive decline (SCD)=32; mild cognitive impairment (MCI)=26; dementia=16) were included. Among all recruited subjects, 31 subjects (36.9%) were A+T+(table 1). The mean age of the subjects was 67.5. 34 (40.8 %) were male.

- No significant associations were found between WMH volume and global 11C-PIB or 18F-T807 standardized uptake value ratio (SUVR) on PET.
- Interestingly, we found that increasing WMH volume significantly correlated with higher plasma p-tau181 level (β = 0.10; 95% C.I.: 0.012 – 0.188; P = 0.03).
- There were no associations between WMH volume and plasma Aβ40, Aβ42, t-tau or NfL levels.

Discussion

No significant association was found between A+T+ and WMH volume in the overall population or within different cognitive diagnostic groups. We found that global PiB uptake correlated with lower WMH volume in dementia patients.

This result may be interpreted by that our population were relative younger than others. Based on previous report, the co-occurrence of CSVD and AD pathology increased with aging.[3]

Similar to our study ,A study with a mixed cohort of AD and MCI ,which were identified from the ADNI database, reported that WMH volume and amyloid uptake were negatively correlated with each other.[5] At the same time, reduced binding of PiB in areas of white matter hyperintensities had been reported before.[6] Further exploration of the "area to area" association between amyloid deposition and WMH need to be conduct.

Plasma p-tau, as a reflection of CSF p-tau 181, it might be more sensitive than PET in the early stage.

Conclusions

Brain WMH volume was associated with plasma p-tau181 level but not with PET tau positivity in the brain. Our results suggest that CSVD burden may contribute to elevated plasma phosphorylated tau in AD, and such change may precede PET-detectable elevated tau burden in the brain.

Table 1. Summary of demographics

Characteristics	Total (n=84)	A+T+ (n=31)	Not A+T+ (n=53)	p value
Age (years), mean (SD)	67.27±7.28	68.10±7.67	66.81±7.08	0.45
Male (n [%])	33(39.28)	10(32.26)	23(43.39)	0.27
Education (years), mean (SD)	9.26±4.50	9.73±4.41	9.02±4.57	0.52
HK-MoCA, median (IQR)	22.33±6.40	18.35±6.79	24.45±5.09	< 0.0001
HKLLT z-score in Trial 4, mean (SD)	-0.73±1.238	-1.80±1.03	-0.18±1.03	< 0.0001
Intracranial volume, mean (SD)	1423.53±133.07	1364.44±137.86	1457.80±118.60	0.002
WMH volume(ml), median (IQR)	1.79(0.69-3.43)	1.92(0.85-3.72)	1.27(0.61-3.30)	0.42
WMH ratio, median (IQR)	0.19(0.05-0.24)	0.20(0.05-0.28)	0.18(0.05-0.21)	0.31
Presence of lacunes, n (%)	5(5.95)	2(6.40)	3(5.66)	0.76
Large cerebral vascular stenosis, (n [%])	9(10.71)	4(12.90)	5(9.43)	0.71
Anterior circulation	5	2	3	0.83
Posterior circulation	6	3	3	0.66

Table 2 Association between ^{11}C- PIB SUVR and WMH volumes

	Outcome		
	Subgroup	logWMH(ML),B(95%CI)	p value
^{11}C- PIB SUVR	HC (n=10)	0.76(-2.96-4.49)	p=0.65
	SCD (n=32)	-0.08(-1.34-1.19)	p=0.90
	MCI (n=26)	-0.53(-1.54-0.48)	p=0.29
	Dementia (n=16)	**-1.76(-2.92- -0.59)**	**p=0.007**
	Total (n=84)	0.01(-0.09-0.10)	P=0.90

Table 3. Association between ^{18}F-T807-SUVR and WMH volumes

	Outcome		
	Subgroup	logWMH(ML),B(95%CI)	p value
^{18}F-T807-SUVR	HC (n=10)	4.17 (-0.70-8.61)	P=0.06
	SCD (n=32)	-0.02(-3.77-2.37)	P=0.65
	MCI (n=26)	-0.55(-2.06-0.97)	P=0.46
	Dementia (n=16)	-0.26(-1.31-0.78)	P=0.59
	Total (n=84)	0.03(-0.04-0.11)	P=0.10

Table 4. Association between plasma biomarkers and WMH volumes

		Outcome	
N=71	Biomarkers	β (95%CI)	P value
LogWMH	Aβ40	0.001(-0.002-0.004)	P=0.535
	Aβ42	0.004 (-0.036-0.045)	P=0.826
	Aβ42/ Aβ40	-1.146 (-10.117-7.825)	P=0.799
	NFL	0.005(-0.009-0.018)	P=0.493
	t-tau	0.006 (-0.092-0.104)	P=0.905
	p-tau 181	**0.100(0.012-0.188)**	**P=0.027**
	P-tau 181/Aβ42	0.526(-0.012-1.064)	P=0.055

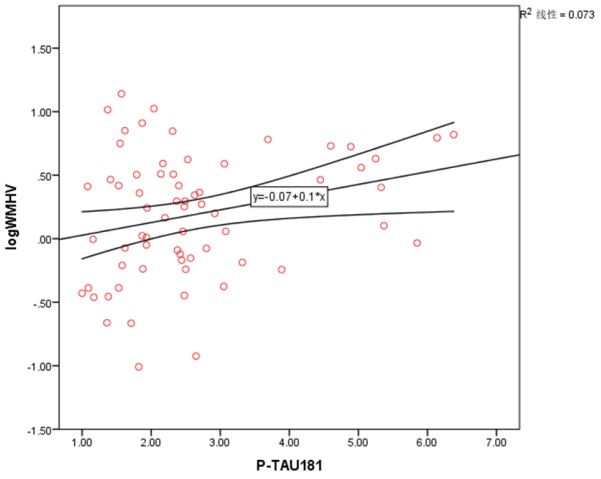

Figure 1. Association between WMH volume and plasma p-tau 181 in all subjects.

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