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Medial Temporal Atrophy in Amyloid-Negative Amnestic Type Dementia Is Associated with High Cerebral White Matter Hyperintensity

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Abstract.
Background: Non-amyloid mechanisms behind neurodegeneration and cognition impairment are unclear. Cerebrovascular disease (CVD) may play an important role in suspected non-Alzheimer's pathophysiology (SNAP), especially in Asia.
Objective: To examine the association between CVD and medial temporal lobe atrophy (MTA) in amyloid-β negative patients with mild amnestic type dementia.
Methods: Thirty-six mild dementia patients with complete neuropsychological, cerebrospinal fluid (CSF) biomarker, and neuroimaging information were included. Only patients with clinically significant MTA were recruited. Patients were categorized based on their CSF Aβ levels. Neuroimaging and neuropsychological variables were analyzed.
Results: Despite comparable MTA between Aβ positive and negative patients, Aβ-negative patients had significantly greater white matter hyperintensities (WMH; Total Fazekas Rating) than their Aβ-positive counterparts (6.42 versus 4.19, $p = 0.03$). A larger proportion of Aβ-negative patients also had severe and confluent WMH. Regression analyses controlling for baseline characteristics yielded consistent results.
Conclusion: Our findings demonstrate that MTA is associated with greater CVD burden among Aβ-negative patients with amnestic type dementia. CVD may be an important mechanism behind hippocampal atrophy. This has implications on clinical management strategies, where measures to reduce CVD may slow neurodegeneration and disease progression.

Keywords: Cerebrovascular disease, medial temporal lobe, neurodegeneration, suspected non-Alzheimer's pathophysiology, white matter hyperintensity, young onset dementia.

INTRODUCTION

The National Institute of Aging–Alzheimer's Association (NIA-AA) has proposed a set of biologically-driven diagnostic guidelines for AD

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[1, 2] to better understand the biological processes underlying the clinical expression of Alzheimer's disease (AD). First published in 2011, the criteria rely on biomarker information (both neuroimaging and biochemical) to diagnose AD, as well as stage disease progression and extent of cognitive impairment. By dichotomizing patients between positive or negative on three separate metrics (A: Amyloid, T: Tau, and N: Neurodegeneration), the NIA-AA framework attributes specific diagnostic labels on patients [3]. In particular, clinical AD dementia patients with neurodegeneration but without amyloidosis are referred to as suspected non-Alzheimer's pathophysiology or SNAP [4, 5].

Several etiologies of SNAP have been proposed. Physiological aging alone has been associated with SNAP, possibly due to synaptic loss [6, 7]. Non-AD pathologies such as TDP-43 proteinopathy and hippocampal sclerosis have also been implicated [8–11]. Additionally, many studies have demonstrated a relationship between neurodegeneration and cerebrovascular disease (CVD). For instance, Werden and colleagues [12] found lower hippocampal volumes among first-ever and recurrent stroke patients. Post-stroke victims also had significantly lower ipsilateral hippocampal volume than healthy controls [13]. Despite the substantial body of literature on SNAP, the non-amyloid mechanisms underlying neurodegeneration and atrophy still remains unspecified.

Among the proposed etiologies of SNAP, CVD is of particular relevance in Asia. Indeed, there is a greater presence of CVD in Asian countries than other parts of the world. The high burden of CVD in Asia has been demonstrated in several studies. In Singapore, severe white matter hyperintensity (WMH; a widely-accepted proxy for CVD) was seen in 28.4% and 39.7% of patients with mild AD and moderate-severe AD, respectively [14]. Similarly, a high prevalence of cerebral white matter lesions has been observed among various cohorts of elderly patients, in Singapore as well as other Asian countries [15, 16].

In the present study, we sought to further examine the role of CVD in SNAP in an Asian cohort. To this end, we selected a cohort with sporadic young-onset dementia of the amnestic type. Younger patients are less likely to have multiple concomitant age-related pathologies that may confound findings. We hypothesized that patients with neurodegeneration and without amyloidosis would have a greater burden of CVD in their brain. More specifically, patients with clinically-significant medial temporal lobe atrophy (MTA) and non-AD-range cerebrospinal fluid (CSF) Aβ would have significantly greater WMH in their structural MRI scans, than their counterparts with AD-range CSF Aβ.

METHODS

Study sample

Patients with mild amnestic type dementia were recruited from a tertiary neurology center (National Neuroscience Institute, Singapore) between 2015–2018, and are part of the Singapore Young-Onset Dementia Cohort (SYNC) Study. Diagnosis of dementia and AD type dementia was based on DSM-5 and NIA-AA criteria [17, 18]. All patients were reviewed by experienced neurologists trained in cognitive neurology. The study included patients with a predominantly amnestic presentation, as well as Clinical Dementia Rating [19] of 1 and Scheltens MTA score [20] of at least 2 on either side of the brain. Only patients with complete CSF, neuroimaging, and neuropsychological information were studied. Patients with neurological or psychiatric comorbidities, as well as a history of alcohol or drug abuse were excluded. Patients with predominant non-amnestic features suggestive of other neurodegenerative conditions (e.g., frontotemporal dementia, Parkinson's disease, or Lewy body dementia) were also excluded. The study was granted approval by Singhealth Centralized Review Board. Informed consent was also sought from each patient according to Declaration of Helsinki and local clinical research regulations.

Measurements

Medical history and demographical characteristics such as the patients' age, gender, and years of education were collected via a standardized interview. All patients went through a lumbar puncture and had their CSF collected and tested for levels of Aβ as well as total and phosphorylated tau proteins. ELISA immunoassays were used to process the CSF specimens, in accordance to prescribed protocol and requirements (INNOTEST tTau Ag, INNOTEST PHOSPHO-TAU(181) and INNOTEST β-AMYLOID(1–42); Innogenetics Inc., Alpharetta, GA).

A standardized battery of neuropsychological assessments was administered to patients by trained research staff. Cognitive information collected examined domains of 1) memory, assessed using

Wechsler Memory Scale Logical Memory delayed recall [21] and Alzheimer's Disease Assessment Scale–Cognitive 10-word delayed recall [22], 2) attention, assessed using Color Trails 1 [23] and Wechsler Adult Intelligence Scale Digit Span Forward and Backward [24], and 3) executive function, assessed using Color Trails 2 [23], Delis-Kaplan Executive Function System Color-Word Interference [25], Frontal Assessment Battery [26], and animal fluency [27]. Measures of global cognition were also taken. They include Mini-Mental State Examination [28], Montreal Cognitive Assessment [27], and Visual Cognitive Assessment Test [29]. Finally, mood was assessed using Geriatric Depression Scale [30].

Patients also underwent a 3T MRI scan (Achieva 3.0; Philips Medical Systems, Best, Netherlands) within six months of clinical and neuropsychological evaluation. Scan specifications include 1) T1-weighted MPRAGE (axial acquisition, 176 slices, matrix size = 256 × 256, voxel size = $1.0 \times 1.0 \times 1.0\,mm^3$, echo time (TE) = 3.2 ms, repetition time (TR) = 7 ms, inversion time (TI) = 850 ms, flip angle = 8°, field of view (FOV)=256×256 mm^2), and 2) T2-weighted FLAIR imaging (170 slices, matrix size = 256 × 256, voxel size = $1.0 \times 1.0 \times 1.0\,mm^3$, TE = 340 ms, TR = 8000 ms, TI = 2400 ms, FOV = $240 \times 240\,mm^2$). The brain scans were visually-rated for MTA using the 0–12 Scheltens Scale [20] on coronal T1-weighted sequences. Scans were also rated for markers of cerebrovascular burden. They include WMH using the 0–12 Fazekas Scale [31] on axial FLAIR sequences; a total score of ≥9 indicated WMH confluence. Lacunes and microbleeds were also quantified based on STRIVE recommendations [32]. All visual-ratings were performed by independent trained raters. Any difference in rating scores between the raters were addressed and resolved by consensus.

Statistical analyses

All statistical analyses were conducted on SPSS Statistics v24 (IBM Corp, Armonk, NY). The study cohort was categorized based on the previously validated cut-off for $A\beta_{1-42}$ [33] into two patient groups—Aβ positive and negative. Demographic, neuroimaging, and cognitive information were summarized (Table 1). In the univariate analysis, group differences were analyzed by χ^2 test of independence for categorical outcomes and Wilcoxon–Mann–Whitney test or independent *t*-test for continuous outcomes. For multivariate analysis, logistic regression was conducted to examine cerebrovascular burden differences across Aβ positive and negative status, while correcting for age, gender, and years of education.

RESULTS

Among 94 patients from the SYNC study cohort with CSF data, 36 met the inclusion criteria. They were categorized into two groups according to their Aβ status. The Aβ-positive group ($n = 16$) consisted of 6 (37.5%) males with a mean age of 57.73 (SD = 5.24) and mean education of 11.0 (SD = 4.06) years. The Aβ-negative group ($n = 20$) consisted of 12 (60.0%) males with a mean age of 56.83 (SD = 6.15) and mean education of 11.5 (SD = 4.72). The Aβ-negative group had significantly greater total WMH Fazekas Scale scores ($M = 6.42$, SD = 2.97) than the Aβ-positive group ($M = 4.19$, SD = 2.93); t(33) = –2.23, $p = 0.03$. The Aβ-negative group also had a significantly more patients with confluent WMH than the Aβ-positive group; $\chi^2(1) = 4.91$, $p = 0.03$. Albeit not reaching significance, the Aβ-negative group had more lacunes ($M = 0.35$, SD = 0.81) than the Aβ-positive group ($M = 0$; SD = 0); t(19) = –1.93, $p = 0.07$. To address possible confounding characteristics, logistic regression was conducted for Fazekas Scale scores and lacune count on Aβ status. Negative Aβ status was significantly associated with greater WMH (β = 0.53, SE = 1.06, $p = 0.005$, 95%CI = 1.06–5.42), as well as lacunes (β = 0.40, SE = 0.25, $p = 0.040$, 95%CI = 0.03–1.04)—while controlling for age, gender, and years of education. These findings demonstrate that patients with clinically-significant MTA who do not have AD-range Aβ have a greater load of silent cerebrovascular burden.

DISCUSSION

Our findings demonstrate that among patients with mild amnestic type dementia having clinically-significant MTA, patients who do not have AD-range Aβ have significantly greater WMH and lacunes. This suggests that cerebrovascular burden may be a possible mechanism or etiology underlying MTA in patients who present with amnestic type dementia.

Present literature suggests the potentiating effect of cerebrovascular burden on the clinical expression of AD in the presence of amyloidosis. Using amyloid-

Table 1
Patients' characteristics and outcomes based on their Aβ status

	Aβ-Positive ($n = 16$)	Aβ-Negative ($n = 20$)
Demographic characteristics		
Age at onset	57.73 (5.24)	56.83 (6.15)
Education (y)	11.0 (4.06)	11.5 (4.72)
Gender (male)	6 (37.5%)	12 (60.0%)
$A\beta_{1-42}$ (pg/mL)	365.25 (82.21)	973.78 (338.32)**
p-Tau (pg/mL)	103.04 (58.59)	50.56 (26.64)**
Total Tau (pg/mL)	724.29 (365.55)	362.63 (215.31)**
Duits' Ratio (Positive)	16 (100.0%)	5 (23.8%)**
Ischemic Heart Disease (yes)	0 (0.0%)	1 (5.0%)
Atrial Fibrillation (yes)	0 (0.0%)	1 (5.0%)
Coronary Artery Disease (yes)	0 (0.0%)	1 (5.0%)
Stroke (yes)	0 (0.0%)	2 (10.0%)
Diabetes Mellitus (yes)	1 (6.3%)	3 (15.0%)
Hypertension (yes)	4 (25.0%)	8 (40.0%)
Hyperlipidemia (yes)	5 (31.3%)	10 (50.0%)
Smoking (yes)	3 (18.8%)	4 (20.0%)
Alcohol (yes)	2 (12.5%)	4 (20.0%)
MMSE	17.36 (5.72)	24.35 (4.05)**
MoCA	14.00 (6.19)	22.47 (5.98)**
VCAT	11.71 (5.84)	19.33 (8.56)**
GDS#	3.77 (2.49)	4.33 (3.37)
Neuroimaging variables		
MTA rating (0–8)	3.94 (0.57)	3.80 (0.52)
WMH rating (0–12)	4.19 (2.93)	6.42 (2.97)*
Confluent WMH (≥9)	0 (0%)	5 (26.3%)*
Lacunes	0 (0)	0.35 (0.81)
Microbleed (Presence of)	0 (0%)	1 (5.6%)
Neuropsychological variables		
Memory		
WMS-IV delayed recall	6.43 (5.94)	4.75 (5.53)
ADAS-Cog delayed recall#	9.00 (1.54)	5.25 (3.82)
Attention		
Color Trail 1#	97.13 (66.16)	88.61 (66.73)
WAIS-IV Digit Span Forward	10.00 (2.80)	8.67 (1.83)
WAIS-IV Digit Span Backward	6.27 (2.91)	7.08 (2.61)
Executive Function		
Color Trail 2#	182.27 (145.12)	139.56 (53.94)
D-KEFS Color-Word; Condition 3: Inhibition#	82.74 (38.34)	81.15 (23.36)
FAB	13.93 (4.92)	14.07 (4.34)
Animal fluency	13.07 (7.25)	11.07 (5.59)

Standard deviation in parentheses unless otherwise written. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; VCAT, Visual Cognitive Assessment Test; GDS, Geriatric Depression Scale; MTA, medial temporal lobe atrophy; WMH, white matter hyperintensity; WMS-IV, Wechsler Memory Scale Logical Memory; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; WAIS-IV, Wechsler Adult Intelligence Scale; D-KEFS, Delis-Kaplan Executive Function System; FAB, Frontal Assessment Battery. *$p < 0.05$, **$p < 0.01$. #Scores are reverse-coded.

PET, a study found an interaction effect between Aβ and WMH. The authors concluded that CVD may provide the 'second hit' necessary for clinical symptoms of AD to manifest [34]. Similarly, another study demonstrated a significant association between Aβ and WMH, and entorhinal cortex volume [35]. Kandiah and colleagues [14] have also previously suggested the synergistic effect of small-vessel CVD and amyloid-tau proteinopathy. According to these findings, CVD is unlikely to result in the clinical presentation of AD without brain amyloid pathology.

However, our findings have demonstrated a direct role of CVD on MTA in patients who present with clinical symptoms suggestive of AD dementia. Supported by a validated CSF Aβ analysis panel, we found a relationship between WMH and MTA, as well as cognitive symptoms in patients who do not have AD-range Aβ. This finding has also been echoed in another local study, which found an association

between WMH and MTA among patients with clinically diagnosed amnestic deficits [14]. We have also previously demonstrated that regional WMH is associated with greater grey matter atrophy in patients with mild cognitive impairment [36]. The present study suggests the direct effect of CVD on clinical symptoms of AD and MTA, in the absence of amyloid pathology.

The current study has also revealed that SNAP is more common than previously acknowledged. Studies have consistently estimated the proportion of SNAP individuals to be about 23–25.9% among clinically normal populations [5, 37]. Among patients with mild cognitive impairment and AD, SNAP varies between 7–39% [38, 39]. In our study, SNAP patients accounted for 56% in a group of mild dementia patients. The discrepancy suggests that the prevalence of SNAP may be influenced by geographic and genetic factors. The Asian cohort in this study may account for the higher prevalence of SNAP.

The findings from our study have obvious implications on clinical settings. The significant role of CVD on neurodegeneration and cognition underscores the need for comprehensive diagnostics for patients with cognitive impairment. Given the overlap between AD and CVD, an MRI alone may not be able to discern between AD and non-AD patients [40]. Likewise, the similarity in cognitive profiles between our Aβ positive and negative groups illustrates the non-specificity of neuropsychological testing. Hence, the inclusion of Aβ evaluation for an accurate AD diagnosis is encouraged—especially in populations with a high burden of CVD.

Given the role of CVD among SNAP patients in Asia, this study also highlights the need to consider and incorporate measures that target the reduction of CVD burden among patients with cognitive impairment. These measures may include therapeutics and interventions that aggressively manage vascular conditions such as diabetes mellitus, hypertension, and hyperlipidemia. Furthermore, several lines of evidence have also established how CVD and WMH are associated with dementia risk and quicker cognitive decline [41, 42]. Including such CVD-related measures will not only benefit SNAP patients, but also individuals that fall on the AD continuum.

Considering the high prevalence (40%) in the Aβ-negative group, hypertension is likely to be the main contributor to small vessel disease among these patients. Besides vascular risk factors, there are likely other factors contributing to the pathogenesis of WMH (e.g., neuroinflammation) among the remaining 60% of the group. This may also be relevant for future management strategies.

To our knowledge, this is one of the first papers exploring the role of CVD in SNAP using an Asian cohort with sporadic young-onset dementia. By investigating younger patients, we are able to lend insight into SNAP without confounding age-related cerebral pathologies such as hippocampal sclerosis and primary age-related tauopathy (PART). Furthermore, the clinical symptoms and presence of objective cognitive impairment in our cohort excludes PART as an underlying mechanism for MTA [43]. This study also takes advantage of a validated CSF Aβ immunoassay to objectively discern between patients with and without Aβ pathology. Remarkably, five Aβ-negative patients were positive for the Duits' ratio (total tau/Aβ) [44] due to their borderline-high total tau levels. While the exact reason is unclear, animal studies from our group have found that cerebral hypoperfusion is associated with elevated tau independent of amyloid [45].

Patients also went through a comprehensive battery of neuropsychological assessments, encompassing multiple domains of cognition. They include amnestic as well as frontal abilities, such as attention and executive function. This enables us to make comparisons or draw similarities in the cognitive profiles of our patients. Of note, the Aβ-positive group had significantly worse-off scores in the Mini-Mental State Examination, Montreal Cognitive Assessment, and Visual Cognitive Assessment Test than the Aβ-negative group. This may be explained by the role of Aβ in disrupting the brain default mode network and in turn, impairing cognition [46, 47]. It is also interesting that domain-specific assessments did not demonstrate consistent results. The effects of Aβ might have been better captured by the higher sensitivity of the screening tests [48].

Limitation-wise, the use of WMH as a proxy for CVD may be contentious. While WMH has been widely used as a measure of small-vessel CVD, there have been reports suggesting that WMH may be, instead, a result of Wallerian degeneration [49]. Nevertheless, we have also demonstrated a higher lacune count in the Aβ-negative group—in support of our CVD hypothesis. Another limitation of our study pertains to the use of visual rating, which may induce some extent of subjectivity into our methodology and conclusions. It will be important to evaluate how our results may differ in similar studies that quantifies neurodegeneration using more objective brain volumetric techniques. Further work is also

needed to fully elucidate the relationship between CVD, neurodegeneration, and amyloid pathology on cognition. Also noteworthy is the generalizability of our study. As the study participants were below 65 years of age, our findings cannot be extended to older patients; additional studies involving older adults are being planned for. Finally, our patients were selected based on their amnestic presentation. It is possible that patients may be misdiagnosed, especially given the heterogeneity and non-specificity of such clinical symptoms.

Conclusion

This study provides evidence that CVD is associated with MTA among patients who do not have brain deposition of Aβ. In Asia, high cerebrovascular burden may be a possible etiology behind neurodegeneration and cognitive impairment. It supports the view that CVD may have a primary role in the clinical expression of amnestic type dementia. This is in contrast with the 'second hit' hypothesis, which suggests that CVD merely potentiates clinical symptoms in the presence of Aβ pathology.

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