AMYLOID-TAU-NEURODEGENERATION PROFILES AND LONGITUDINAL COGNITION IN SPORADIC YOUNG-ONSET DEMENTIA

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Introduction

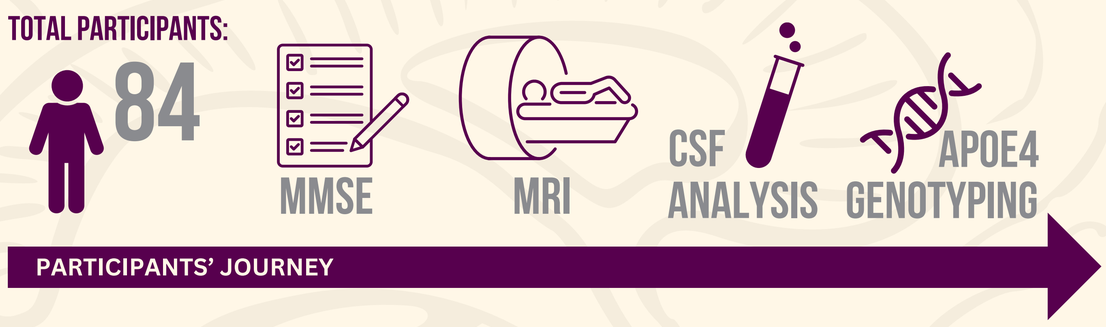
The Amyloid-Tau-Neurodegeneration (ATN) classification enables an unbiased biomarker-based diagnosis of Alzheimer's disease (AD), independent of cognitive status and temporal ordering of AD pathogenic mechanisms [1]. ATN biomarker status is defined by: A, amyloid- deposition; T, tauopathy; N, neurodegeneration.

Examining ATN biomarker profiles across different demographics could hence help guide a change in treatment if required [4,5]. However, the lack of data on young-onset dementia from Asia, including Southeast Asia, illustrated the need for further studies [7,8,10].

Findings from this research demonstrated a high prevalence of Cerebrovascular Disease (CVD) in Asians and hence, it is essential to elucidate its impact on biomarker influence on dementia [13]. Examining biomarkers distribution among young-onset patients with onset below 65 will help understand effects of age-at-onset on pathology and provide important insights into the ATN framework [4,12].

Previous work showed quicker cognitive decline in A-N+, A+N- and A+N+ groups [14,15]. Our prior work showed that CVD moderated the impact of A on cognitive outcomes, but does not have a direct effect on cognition [16]. Therefore, we hypothesised that while A+ patients will show the greatest cognitive decline, presence of CVD+ and T+ among A- patients will also contribute to cognitive decline.

Materials and Methods



A total of 84 participants, diagnosed with young-onset dementia by cognitive neurologists were recruited. They were from the Singapore Young Onset Dementia Cohort and Neurocognition, Imaging and Biomarker Longitudinal Study in Singapore Research studies at NNI.

These participants went through a series of standardised battery of assessments, including the Mini-Mental State Examination (MMSE).

They then underwent MRI imaging (T1 and FLAIR) - assessing medial temporal lobe atrophy. Fazekas scale used to rate subject FLAIR scans for white matter hypersensitivity (WMH)

- Patients were then classified as having confluent or non-confluent WMH based on Staals criteria
- The N profile was assigned based on the medial temporal lobe atrophy (MTA) scores based on the Schelten's scale [29].

They then underwent a lumbar puncture for CSF analysis - testing levels of amyloid-beta, total tau and phosphorylated-tau proteins as well as peripheral blood analysis for APOE4 genotyping.

Classification of ATN profiles:

MEASUREMENT OF	CUT-OFF
A	<550pg/ml
T	>60pg/ml
N	Average ≥ 1

All statistical analyses were performed using R3.6.3 (R Core Team, 2014) with Rstudio (RstudioTeam, 2012) with the lme4, lmertest, sjPlot, ggforce, ggraph, ggthemes, and ggplot2 packages.

Three sets of analysis were done:

FIRST SET	SECOND SET	THIRD SET
Comparing longitudinal MMSE scores and biomarker status (A+N+, A-N+, A-N-) T found to have no effect on longitudinal cognition	Comparing specific influence of A+CVD–T± and CVD+A–T± on longitudinal cognition	Comparing effects of CVD and T among A–N+ patients on longitudinal MMSE scores

Results

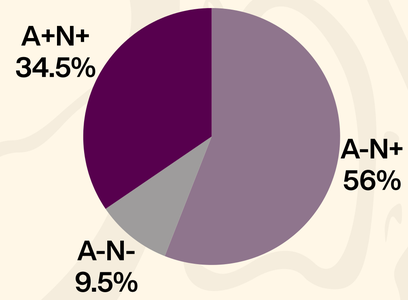


Figure 2: Further breakdown of the participants with A-N+ shows that the majority has CVD+ (40%), followed by T+ (34%) and then participants with T-CVD- (26%)

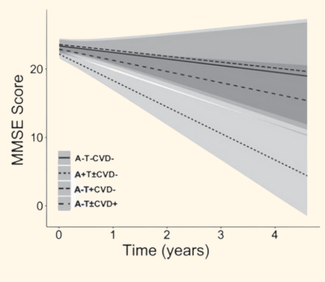


Figure 4: Comparing longitudinal decline in MMSE score in A+ vs A- participants, greatest decline seen in A+N+, followed by A-N+, and A-N-.

Figure 1: Breakdown of the cohort of participants show that the majority of the participants are A-N+ (56%), followed by A+N+ (35%) and A-N- (9%)

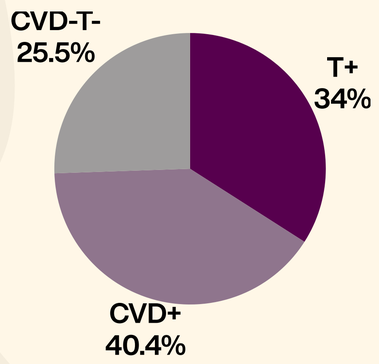
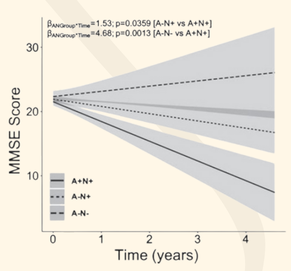


Figure 3: Comparing longitudinal decline in MMSE score, there is a greatest decline in participants with A+T+/-CVD+ . Followed by A-T+/- CVD+, then A-T-CVD- and A+T+/- CVD-



Discussion and Conclusion

Compared to other studies with an A+ frequency of 66%-96.9% [5,35], our study only had a prevalence of 34.5%, likely due to our lower frequency of APOE4 carrier among Southeast Asians [9].

Instead, our largest group had the A-N+ profile, with a higher prevalence of 55.9% compared to other studies at 1.5%-28% [5,35]. Among these patients, CVD+ accounted for the largest group, highlighting the importance of treating CVD risk factors to reduce the risk of Dementia

Regarding MMSE decline, A+ patients had a steeper decline compared to A- patients, supporting past studies indicating a more aggressive course in young-onset Alzheimer's Dementia [51,52]. However, T+ alone had no negative effects on MMSE decline while CVD+ alone demonstrated worse cognitive decline, in line with past studies [49,50]

In conclusion, our study highlighted the importance of preventing and managing cerebrovascular disease in order to reduce the risk of developing dementia. This can be done through lifestyle management and medical therapy which is cannot be said for preventing amyloid deposition.

Limitations:

The study had a relatively small cohort size and short follow up time. We also did not quantify alpha-synuclein and TDP pathology and did not have complete information regarding the duration of disease

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