A biomarker to aid Alzheimer's disease staging: sTREM2 is decreased in Amyloid positive/Tau negative, yet increased once Tau aggregates leading to increased cognitive decline

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Background

The development of high accuracy biofluid assays now allows the use of fluid-based biomarkers into Alzheimer's disease (AD) clinical pathological models. Integration of amyloid and tau biomarkers into AD models has confirmed the centrality of amyloid and tau biology in AD-related neurodegeneration, and to the expression of AD symptoms, such as cognitive decline, and clinical disease progression. AD disease models are now seeking to exploit and use validated fluid biomarkers of other neurodegenerative processes, such as neuroinflammation, to increase understanding of AD beyond amyloid and tau. The soluble triggering receptor expressed on myeloid cells 2 (sTREM2) can be measured in the CSF, providing an opportunity to determine the extent to which measurement of neuroinflammation can add information to amyloid, tau and neurodegeneration based (ATN) models of AD related cognitive decline.

Methods

CSF, pre-clinical Alzheimer's Cognitive Composite (PACC) scores and the Clinical Dementia Rating Sum of Boxes (CDR-SB) were collected among 237 participants from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing. CSF was assessed amongst four ATN groups at baseline: 1) A-/T-/N- (reference group), 2) A+/T±/N± (amyloid+), 3) A-/T±/N± (amyloid-), and 4) A+/T+/N+. sTREM2 was measured using the NeuroToolKit (NTK) panel of exploratory prototype assays (Elecsys® assays; Roche Diagnostics International Ltd, Rotkreuz, Switzerland). Figure 1 shows the distribution of sTREM2 within each of the ATN groups at baseline. Longitudinal change in Aβ (via the centiloid) and cognition given low/high levels of sTREM2 within ATN groups was investigated using linear mixed models (LMMs).

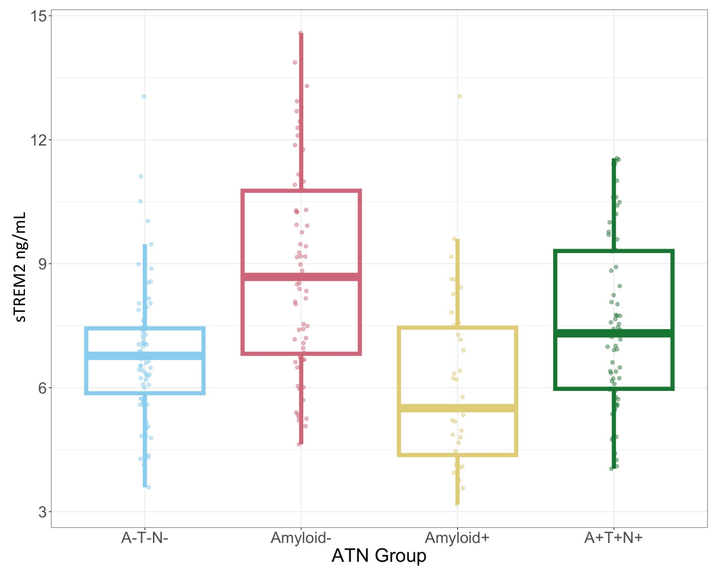

Figure 1: Boxplot at baseline for the sTREM2 biomarker divided by the defined ATN groups (A-T-N-, amyloid+, amyloid-, and A+T+N+).

Results

At baseline, 176 (74%) were Cognitively Unimpaired (CU), 33 (14%) had mild cognitive impairment, and 28 (12%) had AD. ATN groups consisted of 71 (30%) A-T-N-, 64 (27%) amyloid-, 38 (16%) amyloid+ and 64 (27%) A+T+N+. Compared with the A-T-N- group, mean levels of sTREM2 were decreased for the amyloid+ group (A-T-N-: 6.85 [SD: 1.65]; amyloid+: 6.05 [SD: 2.13], p=0.048), were increased substantially in the amyloid- group (8.86 [SD: 2.51], p<0.001) and then increased moderately in the A+T+N+ group (7.57 [SD: 2.11], p=0.029) demonstrating increased sTREM2 associated with T/N+, but decreased in A+ prior to A/T becoming positive (Figure 1). Rates of Aβ accumulation were not different for participants with low/high levels of sTREM2 (p>0.05). In participants who were Aβ+, high levels of baseline sTREM2 was associated with faster cognitive decline when compared to those with low levels of sTREM2 (Figure 2, high β: -0.219 [SE: 0.059], low β: -0.028 [SE: 0.028], p=0.011). Similar relationships were seen for CDR-SB, albeit these were not statistically significant (p=0.168).

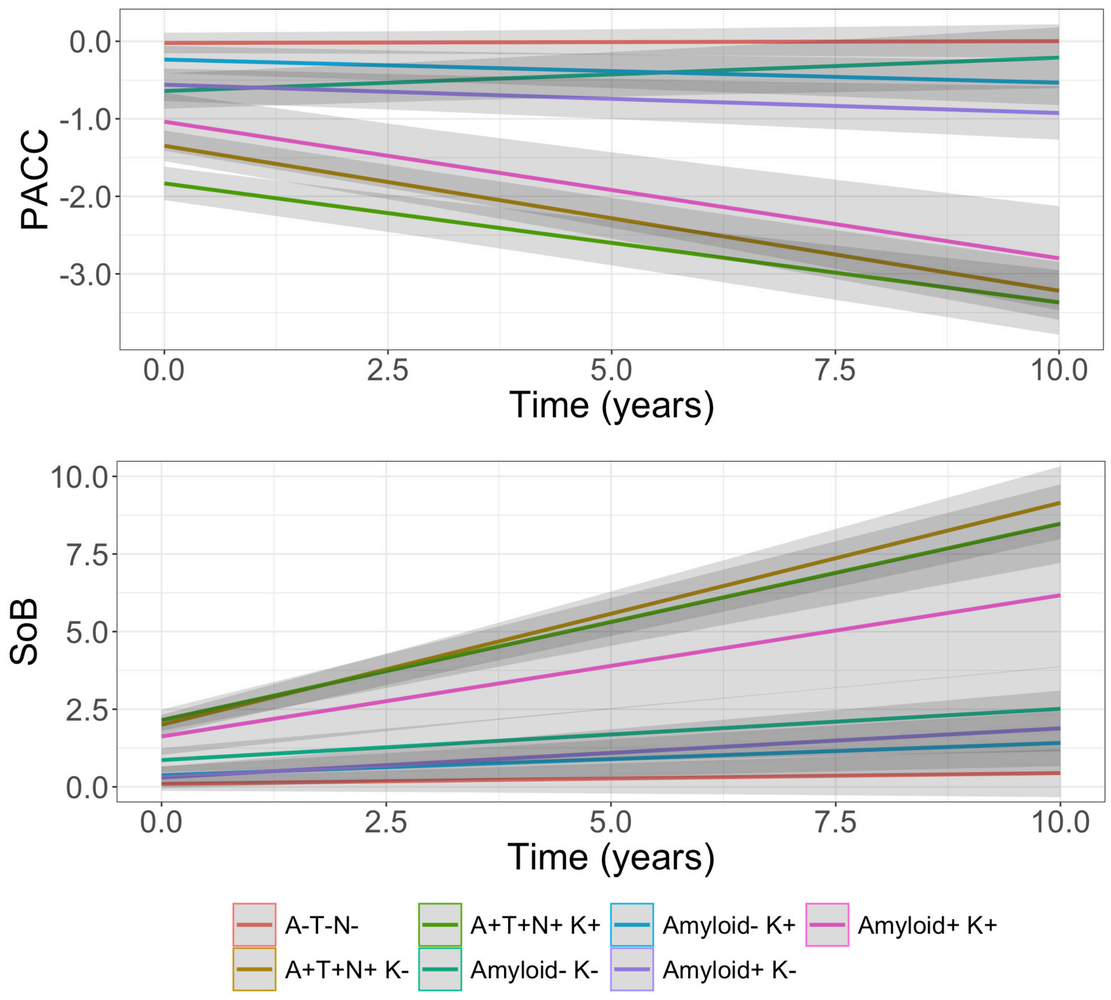

Figure 2: Rates of change in PACC and CDR-SB (or SoB) across ATNK groups. Solid lines represent the slope derived from linear mixed effect models (LMMs). Grey shaded areas represent the 95% confidence interval (CI) of the slope as derived from LMMs. Slope for K- and K+ represent the rate of change as calculated for participants with low and high sTREM2 values within the ATN groups, respectively.

Conclusions

High levels of sTREM2 aligned with T/N+ participants, whilst low levels of sTREM2 aligned with Aβ+ participants prior to accumulating tau or exhibiting signs of neurodegeneration. As sTREM2 increases in Aβ+ participants, levels align with cognitive decline at similar rates observed in A+T+N+ participants. Thus, sTREM2 may be useful in disease staging as an early marker of Aβ positivity, prior to Tau aggregation and neurodegeneration.

FOR FURTHER INFORMATION

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DISCLOSURES

ELECSYS is a trademark of Roche. The Roche NeuroToolKit is a panel of exploratory prototype assays designed to robustly evaluate biomarkers associated with key pathologic events characteristic of AD and other neurological disorders, used for research purposes only and not approved for clinical use.

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