CSF markers YKL40, sTREM2, and α-synuclein enhance the Alzheimer’s disease A/T/N criteria to detect early changes in cognition

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Understand how information from CSF biomarkers from the NTK platform can be used in population studies. Investigate cognitive decline in researchers own cohorts using the ATN criteria.

INTRODUCTION

Alzheimer’s disease (AD) is a multifactorial disease including pre-clinical, prodromal and clinical phases. CSF A/T/N (A42, pTau181, tTau) biomarkers help characterize the biological state of AD.

The primary aim was to assess contributions of eight CSF markers for predicting changes in cognition.

METHODS

CSF from 237 participants (CN: 175(74.3%); MCI: 33(13.9%); AD: 28(11.8%)) of the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging was used to measure A42 (Genti assay), pTau181, and tTau (Elecsys assays; Roche Diagnostics International Ltd, Rotkreuz, Switzerland) along with neuregulin, neurofilament light (NFL), α-synuclein, glial fibrillary acidic protein (GFAP), chitinase-3-like protein 1 (YKL40), soluble triggering receptor expressed on myeloid cells-2 (sTREM2), s100 calcium-binding protein B (s100B), and interleukin-1β (IL-1β) from the NeuroToxIKIT (NTK) panel of exploratory prototype assays (all Roche Diagnostics International Ltd).

NTK biomarker concentrations were measured among each of 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-.

Change in cognition was assessed using the pre-clinical Alzheimer’s cognitive composite (PACC) and the clinical dementia rating sum of boxes (CDR-SB) scores, in all four ATN groups, stratified by low/high NTK biomarker over a minimum of 36 months.

The primary outcome was defined as change in cognition in amyloid+ participants modulated by the addition of NTK markers to ATN groups.

RESULTS

A+/T+/N+ participants had faster cognitive decline on both PACC and CDR-SB over time compared to all other groups (Figure 1A, PACC; Figure 1B, CDR-SB). Within the amyloid+ group, participants with high sTREM2 (K+), with a faster rate of decline in PACC compared to those with low sTREM2 (K−, p=0.04; Figure 1C), whilst participants with high α-synuclein had a faster increase in CDR-SB compared with those with low α-synuclein (p=0.005; Figure 1D). Amongst participants who were A+/T+/N+, those with high YKL40 had a significantly faster rate of decline in PACC (p=0.017; Figure 1E), and a faster increase in CDR-SB (p=0.017; Figure 1F) compared with those who did not YKL40.

CONCLUSIONS

Biomarkers of microglial activation (sTREM2), synuclein oligomers and synuclein metabolism (α-synuclein), and astrocytic activation (YKL40) may be appropriate to discern rates of cognitive change within amyloid+ participants. Findings are being validated in a separate population.

ACKNOWLEDGEMENTS

ELECSYS is a trademark of Roche. The Elecsys Total Tau CSF immunosay is not cleared as a companion diagnostic device. NeuroToxIKIT 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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