Cross-sectional investigation of synaptic markers Neurogranin and BACE1 in CSF from the AIBL study

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Background

• Synaptic dysfunction is a feature of Alzheimer’s disease (AD). Measurement of synaptic proteins may assist with disease staging and can be investigated in relation to amyloid accumulation and the ATN biomarker framework.

• BACE1 is located presynaptically and diseases APP into Aβ fragments. BACE1 has been variably reported to increase or decrease in concentration in CSF along the spectrum of AD progression.1,2 Neurogranin (Ng) is located post-synaptically, and is found in dendritic spines. Ng is involved in neurotrophin signalling and is thought to promote neuronal survival. Ng is reported to decrease in brain tissue, but increases in CSF.3 The Ng/BACE1 ratio is suggested to change in AD and be prognostic for future cognitive decline.4

• Alpha-synuclein is locatedpresynaptically, and aggregates are linked with Parkinson’s disease and other neurodegenerative diseases. Alpha-synuclein comprises a non-amyloid component of amyloid plaques.

• Additionally, soluble Aβ measurement is fraught with preanalytical variability. Alternate protein measures in AD may help with diagnostic accuracy.

Methodology

Participants

n=106 in CSF and matching PET amyloid scans from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study were analysed for CSF synaptic markers. Ng and alpha-synuclein using commercially available ELISA assays (EUROMMIA).

Assay

• BACE1 was developed with ADx401 (SGT) and ADx402 (100K) antibodies.

• Neurogranin C-terminal monoclonal antibody T5 (10K) was used to mammalian antibodies ADx401 (ADxNGCT1) and ADx402 (ADxGT111).

• Alpha-synuclein was used ADx21 and ADx302 antibodies.

• Total tau and Aβ42 were measured using the Roche Elecsys® Gen1 on frozen aliquots.

Biopsy sample

• Fasting CSF was collected by either gravity or aspiration into 15mL PP falcon tubes on wet ice using a Cross sectional investigation of synaptic markers Neurogranin and BACE1 in CSF from the AIBL study

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Results cont.

Synaptic marker levels in relation to PET-amyloid status

• In the ATN subgroup, separation of PET amyloid NEG and POS was equivalent to the A/T/N classification.

• In the amyloid positive group (tau>0.81), the tau/BACE1 (p<0.05) and neuregulin/BACE1 (p<0.05) ratio increased in the presence of worsening clinical symptoms between CN and AD.

• In the CN subgroup, separation of PET amyloid POS prediscline AD (A/T/N was improved by the tau/BACE1 (p=0.05) compared to the tau alone trend (p=0.05)). The neuregulin/BACE1 ratio did not significantly differ between A/T/N groups.

Conclusions

• BACE1 was elevated in all T+ groups, independent of amyloid status. This consistent with recent literature concluding that Ng is more specific for Alzheimer’s disease and Aβ is a marker of synaptic dysfunction and slowly correlates with AD pathology.

• Matching another amyloid status, BACE1 was found to be reduced in presclinical AD (A+/T+) 7 BACE1 was elevated in all instances of T+.

Figure 3. Distribution of CSF markers by A/T/N criteria

Figure 2. Distribution of CSF marker by PET amyloid status and by A/p of preclinical AD.

References


