ELEVATED LEVELS OF SOLUBLE AMYLOID BETA PROTOFIBRILS IN DOWN'S SYNDROME AND ALZHEIMER'S DISEASE

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Aims

Senile plaques in the brain contains amyloid β (Aβ), produced by cleavage of the amyloid precursor protein (APP). The gene encoding APP is located on chromosome 21. Down's syndrome (DS), trisomy of chromosome 21, leads to the propensity to develop Aβ brain pathology followed by impaired function. The present study characterized amyloid species in brains from subjects with DS and Alzheimer's disease (AD) in comparison to non-demented controls (NDC). Binding of BAN2401 (lecanemab), an antibody in phase 3 development for AD with high selectivity for soluble toxic Aβ aggregates, was also investigated.

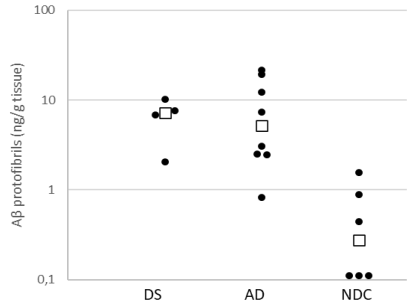
Methods

Cortical brain samples were obtained from The Netherlands Brain Bank (NBB) from individuals with a clinical diagnose of DS (N=4), AD (N=8) or NDC (N=6). In addition, paraffin embedded cortical tissue was obtained from individuals with DS (N=4). Subjects with DS were all of the APO E3/3 genotype, mainly female (71%) with an age range of 58-70 years. The study was approved by the Swedish Ethical Review Authority (no. 2020-00527).

The brain tissues were homogenized in TBS buffer, centrifuged at 16,000 x g, and the supernatants were analyzed for soluble Aβ protofibrils using Mesoscale standard plates coated with the Aβ protofibril selective antibody mAb158 and detected using a biotinylated Aβ specific antibody mAb1C3.

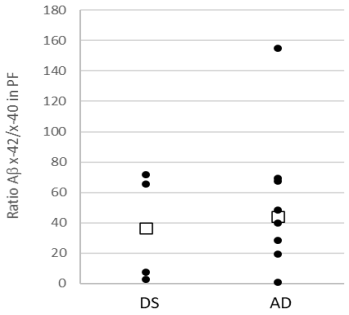
For immunoprecipitation, TBS extracts were incubated with mAb158 and pulled down using Dynabeads. The precipitated Aβ protofibrils were monomerized in 1% SDS at 95°C and analyzed using Mesoscale V-PLEX Aβ Peptide Panel (4G8) Kit.

Soluble Aβ protofibrils – individual (black dots) and median levels (white boxes)



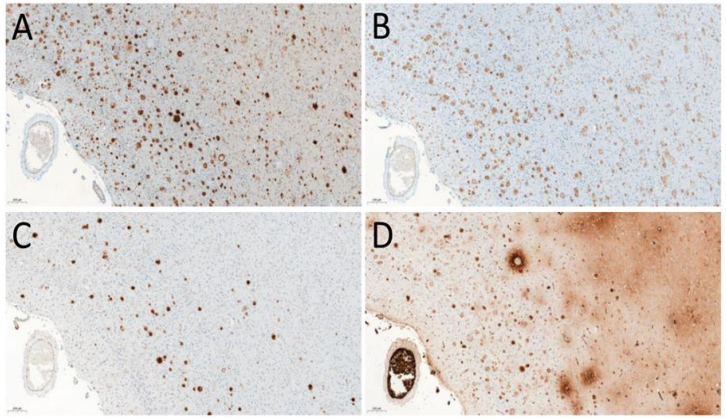
Levels of Aβ protofibrils in brain extracts from DS subjects were shown to be in the same range as those found in AD brain extracts (median 7.2 resp. 5.2 ng/g tissue) and significantly increased (p=0.04 and p=0.009, respectively) compared with brain extracts from NDC subjects (median value 0.3 ng/g tissue).

Aβx-42/Aβx-40 ratios in immunoprecipitated protofibrils - individual (black dots) and median levels (white boxes)



Aβ protofibrils in DS and AD subjects contain approximately 40 times higher levels of Aβx-42 than Aβx-40.

Immunohistochemical staining in cortex from a DS subject.
A) Immunoreactive profiles positive for total Aβ (6E10/4G8)
B) & C) Immunoreactive profiles positive for Aβ1-42 and Aβ1-40, respectively. BioArctic proprietary antibodies.
D) Immunoreactive profiles positive for BAN2401.



Summary and Conclusion

- Significantly elevated levels of soluble Aβ protofibrils were demonstrated in both DS and AD compared to control subjects.
- Binding of BAN2401 to Aβ protofibrils and plaques was for the first time demonstrated in DS subjects.
- The pathological similarities in detected Aβ species across DS and AD subjects and the binding properties of BAN2401 in DS suggest that targeting toxic soluble amyloid species through an antibody with such binding profile may have utility in preserving brain function in adults with DS.
- BAN2401 (lecanemab) is presently in phase 3 clinical development in subjects with early stage AD (ClinicalTrials.gov Identifier: NCT03887455).

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