Longitudinal changes of the synaptic blood marker β-Synuclein in the ADNI cohort and relation to imaging and fluid biomarkers

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Background:

Synaptic degeneration is a major hallmark of AD and the pathological correlate of memory impairment. β-Synuclein is a presynaptic protein and its highly specific expression in the brain makes it a very attractive biomarker candidate in blood to study synaptic degeneration in AD. We and others already showed that β-Synuclein levels in CSF are strongly increased in AD[1–3] similar to other established synaptic markers such as neurogranin or SNAP25. We recently developed a specific mass spectrometry-based method (IP-MS) to measure β-Synuclein also in blood. The method has been extensively validated in terms of intra- and interassay variation, dilution linearity, spike-in recovery, interference from alpha- and gamma synuclein and stability (freeze-thaw, benchtop) ensuring reliable results. We could show that β-Synuclein levels in blood are strongly increased in AD as well. Increased levels are observed already in prodromal AD and we could confirm this observation in patient samples from different collaborators underpinning the robustness of this finding[2,4–6]. β-Synuclein is thus the first synaptic marker in blood reflecting the changes observed in CSF also in blood. Although these cross-sectional studies provided some information about the temporal changes of blood β-Synuclein levels, the longitudinal trajectories of β-Synuclein during different AD stages and its relation to amyloid/tau pathology and brain atrophy have not been studied yet but are essential to further characterize this biomarker and synaptic degeneration in AD

Methods and Procedures

Serum β-synuclein was measured by IP-MS as previously described[4]. In brief, 490µL serum were mixed with an internal standard solution containing recombinant 15N-β-synuclein (rPeptide, Watkinsville, GA, USA) and immunoprecipitated using magnetic beads coupled with an anti-β-synuclein antibody (EP1537Y from Abcam, Cambridge, UK). Beads were washed with

50mM triethylammonium bicarbonate/0.1% n-Dodecyl-β-D-maltoside using a KingFisher Apex instrument and eluted. β-Synuclein was digested by trypsin/LysC (Promega, Walldorf, Germany) and two proteotypic peptides were quantified by LC-MRM (aa46-58 and aa61-85) using an Eksigent MicroLC200, Agilent 1260 pump and Sciex QTRAP6500 mass spectrometer in multiple reaction monitoring (MRM) mode. Calibrators were prepared using recombinant human fulllength β-synuclein (without tags) from rPeptide and the exact concentration of the β-synuclein stock solution was quantified by amino acid analysis (Alphalyse A/S, Odense, Denmark). Calibration range was 2 to 30 pg/mL. Samples were analyzed in a total of 14 runs and serum quality control (QC) samples (low, medium, high) were included in all runs (intraassay CV 0.5–11.5%, interassay CV 8.8-11.1%). Samples were randomly assigned to the different runs and the analysts were blinded to the patient data.

Version Information

Is this an update to a previous existing data set? NO

Data Description

Briefly describe the purpose of the study and the research question(s) the data addresses:

The aim of our study was the measurement of serum β-Synuclein levels in longitudinal samples from CN, MCI and AD patients from the ADNI cohort to investigate group differences, longitudinal changes, relation to amyloid, tau and FDG-PET, brain atrophy (MRI), cognitive impairment and other fluid biomarkers.

How was the cohort for analysis selected? Please explain the criteria used for selection:

To investigate β-synuclein longitudinally in different AD stages and relate it to other pathological mechanisms, we selected patients with MCI and AD dementia as well as a control group for comparison. Requirement for selection was also the availability of follow-up samples at 12, 24, 36 and 48 months and data on imaging, fluid and clinical biomarkers.

What biases might exist within the selected cohort? Please explain:

Are there any limitations to the data that should be noted? (e.g. missing data, incomplete measures, etc.):

Measurements failed for 2 (out of 900) samples and reanalysis was not possible because there was not enough sample volume. Thus, there are two missing values in the dataset.

User Guidance

Is there any existing literature that you believe would be particularly helpful for investigators who are interested in understanding and working with this data set? If so, please provide DOI links here:

Oeckl P, Halbgebauer S, Anderl-Straub S, von Arnim CAF, Diehl-Schmid J, Froelich L, Grimmer T, Hausner L, Denk J, Jahn H, Steinacker P, Weishaupt JH, Ludolph AC, Otto M. Targeted Mass Spectrometry Suggests Beta-Synuclein as Synaptic Blood Marker in Alzheimer's Disease. J Proteome Res. 2020 Mar 6;19(3):1310-1318. doi: 10.1021/acs.jproteome.9b00824.

Are there are any other tables in the ADNI data set that are closely related to this one? If so, please note their titles here and provide a brief explanation of how they are related:

NO

Please provide any further guidance or suggestions for how the data should be used by investigators, or any pitfalls users should be aware of so that data is not used incorrectly:
NO

References

1. Oeckl, P. *et al.* Alpha-, beta-, and gamma-synuclein quantification in cerebrospinal fluid by multiple reaction monitoring reveals increased concentrations in Alzheimer's and creutzfeldt-jakob disease but no alteration in synucleinopathies. *Mol. Cell. Proteomics* **15**, 3126–3138 (2016).
2. Oeckl, P. *et al.* Targeted Mass Spectrometry Suggests Beta-Synuclein as Synaptic Blood Marker in Alzheimer's Disease. *J. Proteome Res.* **19**, 1310–1318 (2020).
3. Halbgebauer, S. *et al.* Beta-synuclein in cerebrospinal fluid as an early diagnostic marker of Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **92**, 349–356 (2021).
4. Oeckl, P. *et al.* Relationship of serum beta-synuclein with blood biomarkers and brain atrophy. *Alzheimer's Dement.* **19**, 1358–1371 (2023).
5. Oeckl, P. *et al.* Blood β-synuclein is related to amyloid PET positivity in memory clinic patients. *Alzheimer's Dement.* **19**, 4896–4907 (2023).
6. Oeckl, P. *et al.* Higher plasma β-synuclein indicates early synaptic degeneration in Alzheimer's disease. *Alzheimer's Dement.* **19**, 5095–5102 (2023).

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