Cerebrospinal Fluid Panel of Synaptic Proteins in Cerebral Amyloid Angiopathy and Alzheimer’s Disease

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Accepted 5 January 2023
Pre-press 6 February 2023

Abstract

Background: Alzheimer’s disease (AD) and cerebral amyloid angiopathy (CAA) share pathogenic pathways related to amyloid-β deposition. Whereas AD is known to affect synaptic function, such an association for CAA remains yet unknown.

Objective: We therefore aimed to investigate synaptic dysfunction in CAA.

Methods: Multiple reaction monitoring mass spectrometry was used to quantify cerebrospinal fluid (CSF) concentrations of 15 synaptic proteins in CAA and AD patients, and age- and sex-matched cognitively unimpaired controls.

Results: We included 25 patients with CAA, 49 patients with AD, and 25 controls. Only neuronal pentraxin-2 levels were decreased in the CSF of CAA patients compared with controls (p = 0.04). CSF concentrations of 12 other synaptic proteins were all increased in AD compared with CAA or controls (all p ≤ 0.01) and were unchanged between CAA and controls. Synaptic protein concentrations in the subgroup of CAA patients positive for AD biomarkers (CAA/ATN+; n = 6) were similar to AD patients, while levels in CAA/ATN- (n = 19) were comparable with those in controls. A regression model including all synaptic proteins differentiated CAA from AD at high accuracy levels (area under the curve 0.987).

Conclusion: In contrast to AD, synaptic CSF biomarkers were found to be largely unchanged in CAA. Moreover, concomitant AD pathology in CAA is associated with abnormal synaptic protein levels. Impaired synaptic function in AD was confirmed in this independent cohort. Our findings support an apparent differential involvement of synaptic dysfunction in CAA and AD and may reflect distinct pathological mechanisms.

Keywords: Alzheimer’s disease, biomarkers, cerebral amyloid angiopathy, cerebrospinal fluid, synaptic pathology

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INTRODUCTION

Deposition of abnormally folded amyloid-β (Aβ) peptides is a common pathologic mechanism in both Alzheimer’s disease (AD) and cerebral amyloid angiopathy (CAA). In AD, Aβ deposits as plaques in the brain parenchyma, whereas in CAA, Aβ aggregates are found within cortical and leptomeningeal blood vessel walls [1, 2]. Involvement of the same protein fits the high comorbidity of moderate-to-severe CAA observed in almost 50% of AD patients [3]. Symptoms of cognitive impairment and dementia are central to both diseases.

Cognitive dysfunction correlates strongly with synaptotoxicity in AD [2, 4], where synaptic loss is recognized as one of the earliest detectable events in AD pathogenesis. Elevated levels of synaptotagmin-1, growth-associated protein 43, synaptosomal-associated protein 25, and neurogranin have repeatedly been demonstrated in the cerebrospinal fluid (CSF) of AD patients [5–7]. Similarly, increased levels of synaptic proteins involved in vesicular transport and synaptic stability have been observed in patients with mild cognitive impairment, particularly those who progressed to AD [8]. A meta-analysis confirmed widespread synaptic loss in AD, with endosomal pathways, vesicular assembly mechanisms, glutamate receptors, and axonal transport being primarily affected [9]. Liquid chromatography-mass spectrometry (LC-MS) methods demonstrated that CSF levels of beta- and gamma-synuclein, neurogranin, phosphatidyethanolamine-binding protein-1 (PEBP-1), 14–3–3 proteins, and neuronal pentraxins levels were altered in AD compared with healthy controls [10], suggesting these proteins may serve as synaptic biomarkers for AD.

In contrast to AD, possible synaptic dysfunction in CAA remains understudied. Vascular amyloid might inflict synaptic degeneration, since a mouse model of non-Aβ Danish CAA demonstrated impaired inhibitory synaptic pathways, and increased tau hyperphosphorylation and misfolding [11, 12]. In contrast, it has previously been demonstrated that CSF levels of the synaptic protein neurogranin are similar in controls and patients with CAA [13]. Studying synaptic dysfunction in CAA may elucidate underlying mechanisms leading to cognitive decline in CAA and reveal yet unknown interactions or differences with AD pathophysiology.

We therefore aimed to investigate synaptic dysfunction in CAA by employing the analysis of a synaptic protein panel in CSF in cohorts including patients with clinical CAA and AD, and controls. Furthermore, we aimed to explore the relation of synaptic protein CSF levels to cerebrovascular imaging markers and cognitive decline in CAA.

MATERIALS AND METHODS

Cohorts

We included CSF samples from 25 patients with probable CAA, 49 patients with AD, and 25 control participants from the Radboud University Medical Center (Radboudumc, Nijmegen, the Netherlands; Table). CSF was collected via lumbar puncture according to a standardized protocol. See the Supplementary Material for details on CSF sample collection and ethical statements for all study participants.

Probable CAA diagnosis was obtained via magnetic resonance imaging (MRI) analysis based on the modified Boston criteria [14]. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) in 21 of the CAA patients [15]. AD patients had a positive amyloid/pathological tau/neurodegeneration (ATN) biomarker profile [16, 17], as defined by CSF Aβ42 <659 pg/ml (A+), phosphorylated tau181 > 64 pg/ml (T+), and total tau > 400 pg/ml (N+) quantified by automated immunoassays using a Lumipulse apparatus (Fujirebio, Ghent, Belgium). Details on the selection of control participants are provided in the Supplementary Material. Age- and sex-matched control participants were cognitively unimpaired. Information on CAA imaging markers was available neither for AD patients, nor for controls.

Magnetic resonance imaging

All CAA patients underwent an MRI scan of the brain. Of those, twenty participants underwent a 3.0 Tesla MRI scan (Siemens Magnetom Prisma, Siemens Healthineers, Erlangen, Germany) using a 32-channel head coil. Participants were examined using a comprehensive protocol, and we analyzed the 3D multi-echo gradient echo T2∗-weighted sequence (voxel size 0.8 × 0.8 × 0.8 mm), the 3D T2-weighted sequence (voxel size 0.8 × 0.8 × 0.8 mm), and 3D fluid-attenuated inversion recovery (FLAIR) sequence (voxel size 0.8 × 0.8 × 0.8 mm). Magnitude and phase data from the multi-echo gradient sequence was processed to a susceptibility-weighted imaging (SWI) using the Contrast-weighted,
The panel of synaptic biomarkers for simultaneous quantification included 14–3–3 epsilon, 14–3–3 eta, 14–3–3 zeta/delta, activating protein-2 (AP-2) complex subunit beta, complexin-2, beta-synuclein, gamma-synuclein, neurogranin, neuronal pentraxin-1 (NPTX1), neuronal pentraxin-2 (NPTX2), neuronal pentraxin receptor (NPTXR), rab GDP dissociation inhibitor (GDI) alpha, PEBP-1, syntaxin-1B, and syntaxin-7. The applied methodology has been described in detail elsewhere [10]. See Supplementary Table 1 for all analyzed peptides. In brief, 100 μL CSF was mixed with stable isotope labeled peptide standards (internal standard), followed by sample preparation in a consecutive four-step process consisting of reduction, alkylation, tryptic digestion, and purification by solid-phase extraction. For multiple reaction monitoring MS quantitation, a micro-high-performance LC-MS system (6495 Triple Quadrupole LC/MS system, Agilent Technologies, Santa Clara, CA, USA), equipped with a Hypersil Gold reversed phase column (dim. 100 × 2.1 mm, particle size 1.9 μm, Thermo Fisher Scientific, Waltham, MA, USA) was used. Pooled CSF samples were used as quality control and injected at regular intervals to monitor assay performance over time and to assess inter- and intra-assay variation.

Data processing and statistical analyses

Skyline version 20.1 (MacCoss Lab, University of Washington, USA) was used for chromatographic spectra peak assessment and adjustment. Ratio of the total peak areas for each peptide and corresponding internal standard, multiplied by the amount of standard added per μL CSF, was used as relative peptide concentration for each peptide.

Data was analyzed using GraphPad Prism software version 9.0.0 (GraphPad Software, Inc., San Diego, CA, USA). Shapiro-Wilk tests were used to analyze data normality. Parametric data were analyzed with a Student’s t-test or analysis of variance with Bonferroni’s post hoc test. Non-parametric data were analyzed with a Kruskal-Wallis with Dunn’s post hoc test. Categorical variables were analyzed with a Chi-square test. For proteins with multiple quantified peptides, the peptide with the lowest coefficients of variation (CV) was used for statistical analysis (Supplementary Table 1). Multiple logistic regression and receiver operating curve analyses were used to analyze diagnostic accuracy in differentiating CAA from AD including all synaptic proteins. Spearman rank correlations were used to evaluate associations between MoCA score and imaging markers with synaptic protein concentrations in

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RESULTS

The intra-assay CV was < 10% and the inter-assay CV < 14% for all peptides (Supplementary Table 1).

Synaptic protein differences

NPTX2 levels were decreased in CAA compared with controls ($p = 0.04$), but not in AD (Fig. 1 and Supplementary Table 2). All other synaptic proteins were present at similar concentrations in CAA and controls.

Twelve synaptic proteins displayed higher levels in AD compared with controls ($p < 0.01$ for syntaxin-7, gamma-synuclein, and 14–3–3 eta; $p < 0.001$ for syntaxin-1B, complexin-2, AP-2 complex subunit beta; $p < 0.0001$ for beta-synuclein, rab GDI alpha, PEBP-1, neurogranin, 14–3–3 epsilon and zeta/delta). Compared to CAA, levels in AD were also higher for gamma-synuclein ($p < 0.01$), syntaxin-1B, complexin-2, AP-2 complex subunit beta (all $p < 0.001$), beta-synuclein, rab GDI alpha, PEBP-1, neurogranin, 14–3–3 epsilon and zeta/delta (all $p < 0.0001$). Levels of NPTX1 and NPTXR were similar for all groups. All synaptic proteins combined differentiated CAA from AD with an area under the curve of 0.987 (95% confidence interval: 0.97–1.00, $p < 0.0001$).

Correlations with MoCA and imaging markers in CAA

Both NPTX2 ($r_s = 0.64$, $p = 0.002$) and NPTXR ($r_s = 0.49$, $p = 0.03$) correlated with MoCA score in CAA (Fig. 2). None of the imaging parameters correlated with any of the synaptic proteins.

Exploratory analysis including CAA/ATN+ and CAA/ATN−

When we stratified CAA patients according to their ATN biomarker status, six CAA patients were AD biomarker positive (CAA/ATN+) and nineteen were negative (CAA/ATN−). The exploratory analysis showed that compared with CAA/ATN−, levels in AD were increased for NPTX1 ($p < 0.05$), gamma-synuclein, syntaxin-7 (both $p < 0.01$), 14–3–3 epsilon, AP-2 complex subunit beta, complexin-2, PEBP-1, syntaxin-1B (all $p < 0.001$), 14–3–3 zeta/delta, beta-synuclein, neurogranin, and rab GDI alpha (all $p < 0.0001$; Supplementary Figure 1).

Five synaptic proteins displayed increased levels in CAA/ATN+ compared with CAA/ATN− ($p < 0.05$ for 14–3–3 zeta/delta, gamma-synuclein, neurogranin, and rab GDI alpha; $p < 0.01$ for beta-synuclein).

Levels of 14–3–3 epsilon and zeta/delta, and beta-synuclein were increased in CAA/ATN+ compared with controls (all $p < 0.05$). All synaptic proteins were present at similar concentrations in CAA/ATN− and controls, and in CAA/ATN+ and AD.

MoCA scores and cerebrovascular imaging markers did not differ between CAA/ATN+ and CAA/ATN− (Supplementary Table 3).

Table 1

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Controls</th>
<th>AD</th>
<th>CAA</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>25</td>
<td>49</td>
<td>25</td>
<td>0.10</td>
</tr>
<tr>
<td>Age (y)</td>
<td>71.9 ± 7.3</td>
<td>69.6 ± 7.2</td>
<td>73.2 ± 6.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex, M/F (% male)</td>
<td>12/13 (48%)</td>
<td>22/27 (45%)</td>
<td>13/12 (52%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Aβ42 (pg/ml)</td>
<td>10,876 [6,419–14,737]</td>
<td>9,837 [7,574–11,727]</td>
<td>7,530 [6,125–8,391]</td>
<td>0.002</td>
</tr>
<tr>
<td>Aβ42</td>
<td>641 [530–1,116]</td>
<td>419 [307–482]</td>
<td>346 [288–410]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>t-tau</td>
<td>256 [177–387]</td>
<td>856 [726–952]</td>
<td>391 [272–537]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>p-tau141</td>
<td>132 [115–148]</td>
<td>47.2 [34.6–61.8]</td>
<td>42 [641 [530–1,116]</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Both NPTX2 ($r_s = 0.64$, $p = 0.002$) and NPTXR ($r_s = 0.49$, $p = 0.03$) correlated with MoCA score in CAA (Fig. 2). None of the imaging parameters correlated with any of the synaptic proteins.

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 age is presented as means ± standard deviations. Aβ and tau levels are presented as medians [interquartile range]. Bold $p$ values indicate statistical significance. Aβ, amyloid-β peptide; AD, Alzheimer’s disease; CAA, cerebral amyloid angiopathy; F, female; M, male; p-tau141, phosphorylated tau; t-tau, total tau. aAnalysis of variance with Bonferroni’s post hoc test. bChi-square test. cKruskal-Wallis test with Dunn’s post hoc test. dStatistically significant for AD versus CAA eStatistically significant for controls versus AD fStatistically significant for controls versus CAA.
Fig. 1. Cerebrospinal fluid levels of synaptic proteins in controls, AD, and CAA. Concentrations (fmol/ml) were obtained after multiple reaction monitoring analysis of the synaptic proteins. Statistical comparison was performed with analysis of variance with Bonferroni’s post hoc test, or Kruskal-Wallis with Dunn’s post hoc test, as appropriate. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001. Median values and interquartile range are indicated. AD, Alzheimer’s disease; AP-2, activating protein 2; CAA, cerebral amyloid angiopathy; GDI, GDP dissociation inhibitor; PEBP-1, phosphatidylethanolamine-binding protein 1.
In this study, we demonstrated a decrease of NPTX2 concentrations in the CSF of CAA patients, but other synaptic protein levels were unchanged in CAA. Moreover, we were able to confirm previous findings of synaptic degeneration in AD in our cohort. The synaptic panel differentiated CAA from AD at high accuracy levels. Finally, the exploratory analysis regarding CAA subgroups showed that CAA/ATN+ patients have a synaptic protein profile resembling that of AD patients, whereas CAA/ATN- were similar to controls.

Several synaptic proteins displayed higher CSF levels in AD as compared with both CAA and controls, coinciding with previous observations. Synapse loss is one of the main neurodegenerative mechanisms in AD, preceding indicators of neuronal death [25] and presenting during the preclinical disease stage [8]. Since synaptotoxicity and cognitive decline correlate well [2, 4], synaptic protein CSF levels may serve as indicators of disease severity in AD. In contrast to this synaptotoxicity in AD driven by parenchymal Aβ, growing evidence suggests that neurodegeneration induced by vascular Aβ in CAA more prominently presents as ischemic brain injury and vascular integrity loss, leading to progressive atrophy and cognitive decline [1, 26]. Thus, unchanged synaptic proteins levels in CAA might reflect mechanistic differences in the pathological pathways of AD and CAA. The observed similar synaptic protein concentrations in CAA/ATN- and controls underline the lack of synaptic loss in CAA in the absence of AD pathology.

Decreased levels of NPTXs secreted into the synaptic cleft, such as NPTX2, could reflect a different mechanisms of synaptic dysfunction in patients with CAA, in the form of inducing short-term or long-term depression by interacting with AMPA receptors to modulate synaptic plasticity [27, 28]. NPTX2 CSF levels correlate the best with cognitive status compared with other synaptic markers [10, 29]. Decreased NPTX2 CSF levels were previously reported in AD, however differentially expressed pentraxins have also been associated with other neurodegenerative diseases, including multiple sclerosis, frontotemporal dementia, and Parkinson’s disease [27, 29]. Moreover, NPTX2 levels have been associated with processes like neuroinflammatory responses [30] and blood-brain barrier dysfunction [31]. Although NPTX2 levels correlated with MoCA scores in CAA, it is questionable whether the lowered NPTX2 levels in CAA display disease-specific synaptotoxicity, or rather reflect universal neurodegeneration. Additionally, synaptic protein levels of CAA/ATN+ resembled that of AD patients, indi-
cating that AD pathology may be driving synaptic dysfunction. As opposed to NPTXs, all other synaptic proteins included in the current study are located at presynaptic and postsynaptic terminals, and not secreted into the synaptic cleft [10]. Unchanged concentrations of these synaptic proteins might consequently point to more conserved synapses in CAA, in contrast to what is commonly seen in AD. Of all currently investigated synaptic proteins, only neurogranin was previously studied in patients with CAA [13], yielding CSF concentrations similar to controls like in our study, further corroborating our hypothesis on more conserved synapses in CAA than AD.

Our results should be considered in light of several limitations. The relatively small sample sizes may lead to a limited study power; however, we could confirm previously reported results of altered levels in AD compared with controls. The APOE e4 allele is a known major risk factor for the development of both vascular and parenchymal Aβ deposits [2], but APOE genotype status was not available to include as a confounder. Moreover, AD diagnosis was solely based on ATN-biomarker status, without knowledge of clinical phenotype. Finally, general cognitive assessment scores and MRI data were only available for patients with CAA. A major strength includes using a robust and validated LC-MS quantification method, with high sensitivity and selectivity for the targeted synaptic proteins.

To conclude, our findings show that synaptic functioning may be more conserved in CAA compared with AD. CSF levels of synaptic markers could serve as biomarkers of synaptic pathology in AD. Our findings support a possible differential involvement of synaptic dysfunction in CAA and AD, which is particularly pronounced in the presence of AD pathology. However, since CSF levels are an indirect reflection of pathological processes occurring in the central nervous system, neuropathology studies assessing regional differences will aid in verifying the lack of synaptotoxicity in CAA. Furthermore, longitudinal studies including cognitive assessments are warranted to examine the association of synaptic dysfunction with disease severity.

**ACKNOWLEDGMENTS**

We thank Hugo van Berckel-Smit for his help with rating the MRIs.

**FUNDING**

This work was supported by the Eivind and Elsa K: Son Sylvan Foundation, the Märtä and Gustaf Ågren Foundation, the Herbert and Karin Jacobsson Foundation, the Gun and Bertil Stohne Foundation, the Foundation for Gamla Tjänarinnor, the Felix Neubergh Foundation, Demensfonden, Rune and Ulla Almlov Foundation, an anonymous donor and a grant from The Galen and Hilary Weston Foundation (NR170024). MMV is supported by the BIONIC project (no. 733050822, which has been made possible by ZonMW as part of ‘Memorabel’, the research and innovation program for dementia, as part of the Dutch national ‘Deltaplan for Dementia’: zonmw.nl/dementiaresearch) and the CAFÉ project (the National Institutes of Health, USA, grant number 5R01NS104147-02). The BIONIC project is a consortium of Radboudumc, LUMC, ADX Neurosciences, and Rhode Island University. CJK receives funding for research outside the submitted work of the Netherlands Cardiovascular Research Initiative, which is supported by the Dutch Heart Foundation, CVON2015–01: CONTRAST, and the support of the Brain Foundation Netherlands (HA2015.01.06). CONTRAST is additionally financed by the Ministry of Economic Affairs by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships (LSHM17016) and was funded in part through unrestricted funding by Stryker, Medtronic and Cerenevoy. The funding sources were not involved in study design, monitoring, data collection, statistical analyses, interpretation of results, or manuscript writing; Radboudumc and Erasmus MC received additional unrestricted funding on behalf of CONTRAST, for the execution of the Dutch ICH Surgery Trial pilot study and for the Dutch ICH Surgery Trial from Penumbra Inc. FHBMS is supported by a senior clinical scientist grant of the Dutch Heart Foundation (grant 2019T060).

HZ is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (#681712), Swedish State Support for Clinical Research (#ALFGBG-720931), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer’s Association (#ADSF-21-831376-C, #ADSF-21-831381-C and #ADSF-21-831377-C), the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2019-0228),
the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADe), European Union Joint Program for Neurodegenerative Disorders (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003). KB is supported by the Swedish Research Council (#2017-00915), the Alzheimer Drug Discovery Foundation (ADDF), USA (#RDAPB-201809-2016615), the Swedish Alzheimer Foundation (#AF-742881), Hjärnfonden, Sweden (#FO2017-0243), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (#ALFGBG-715986), European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236), and the Alzheimer’s Association 2021 Zenith Award (ZEN-21-848495). JG is supported by Alzheimefonden (AF-930934) and the Foundation of Gamla Tjänarinnor. AB is supported by European Union Joint Program for Neurodegenerative Disorders (“PreSSAD” JPND2021-650-272).

CONFLICT OF INTEREST

HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Artery Therapeutics, AZTherapeutics, CogRx, Denali, Eisai, Nervgen, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. MMV serves as a consultant for Vico. The other authors declare no conflict of interest.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-220977.

REFERENCES


