Presence of Cerebral Amyloid Modulates Phenotype & Pattern of Neurodegeneration in Early Parkinson’s Disease

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Background
• Over 25% of Parkinson’s disease (PD) patients present with a mild cognitive impairment and approximately 80% of PD eventually develop dementia.
• Neuropathological studies suggest that amyloid is present in > 50% of PD patients.
• Little is known about the impact of amyloid on the presentation of early (<2 years) PD (ePD).
• We evaluate how cerebrospinal fluid (CSF) evidence of amyloid is associated with CSF, genetic, neuropsychological, and imaging phenotypes.

Participants & Methods
• We evaluated 369 drug-naive and early diagnosis ePD patients & 174 healthy controls.
• Data were obtained from the Parkinson’s Progression Markers Initiative (PPMI) database.
• CSF amyloid-beta levels were transformed using a previously reported linear regression procedure. A cutoff of >189 pg/mL was used to define amyloid-negative (Control-, ePD-) and amyloid-positive (Control+, ePD+) subgroups.
• ANOVAs and post hoc t-tests were used for statistical analysis.

Results
• 17% of ePD and 17% of Controls have CSF evidence of cerebral amyloidosis (Aβ+).
• Aβ+ status is associated with older age for ePD and Controls.
• CSF analyses revealed that ePD- have lower p-tau and alpha-synuclein relative to Controls; ePD+ have reduced t-tau, p-tau, and alpha-synuclein CSF relative to all other groups.
• Aβ+ status is associated with APOE ε4 carrier status in ePD and Controls.
• ePD have reduced neuropsychological performance on MOCA, HVLT memory, and Symbol-Digit Matching relative to Controls. ePD+ are also selectively impaired relative to ePD- on symbol-digit matching and verbal category fluency with borderline reduced performance on delayed and intermediate recall.
• Imaging analyses relative to Control- revealed overlapping disease for ePD- and ePD+ in anterior medial temporal and frontal cortex.
• Direct subgroup imaging comparisons revealed a more cortical and frontal distribution of disease for ePD+ relative to ePD- and a more deep and putamen distribution of disease for ePD- relative to ePD+.

Conclusions
• Our findings suggest that cerebral amyloidosis, as measured with CSF, yields a unique phenotype of ePD+ that includes increased difficulty with executive and processing speed tasks that are mediated in part by increased frontal cortex disease.
• As previously suggested, age and APOE ε4 status appear to increase risk of Aβ+ but this appears independent of Control or PD status.
• Future work should address whether cerebral amyloid has a synergistic interaction with alpha-synuclein to yield a more aggressive form of PD as suggested by the even lower (more abnormal) CSF alpha-synuclein levels in ePD+.

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Measure | Control- | Control+ | ePD- | ePD+ | ANOVA
--- | --- | --- | --- | --- | ---
N | 145 | 29 | 309 | 61 | ~
Gender | 50 F / 95 M | 10 F / 19 M | 109 F / 200 M | 16 F / 45 M | X=1.86 (p=0.6011)
Age | 59.55 (10.82) | 62.90 (14.42) | 60.17 (9.94) | 65.3 (8.3) | F=20.88 (p=0.0001)
Cerebrospinal Fluid | | | | |
Transformed Aβ-42 | 252 (34.90) | 171 (26.66) | 249 (31.67) | 178 (26.84) | F=225.66 (p<0.0001)
Total Tau | 50 (21.62) | 66 (47.94) | 46 (16.72) | 39 (25.05) | F=25.08 (p=0.0001)
Phosphorylated Tau | 18 (10.64) | 21 (17.38) | 16 (9.61) | 13 (9.51) | F=24.13 (p<0.0001)
Alpha-Synuclein | 2214 (976) | 2235 (1645) | 1942 (795) | 1435 (634) | F=36.30 (p<0.0001)
Genetics | | | | |
APOE ε4 Carrier (+/-) | 116 / 29 | 12 / 17 | 235 / 74 | 36 / 25 | F=32.21 (p<0.0001)
APOE ε4 Alleles (0/1/2) | 116 / 28 / 1 | 12 / 14 / 3 | 235 / 69 / 5 | 36 / 22 / 3 | F=26.35 (p<0.0001)
Neuropsychological | MOCA | 28.19 (1.11) | 28.28 (1.13) | 27.22 (2.2) | 26.93 (2.41) | F=24.17 (p<0.0001)
HVLT Delayed Recall | 6.97 (1.79) | 6.48 (1.64) | 6.46 (1.80) | 5.90 (1.66) | F=16.29 (p=0.0010)
HVLT Recognition | 9.33 (2.47) | 9.03 (1.80) | 8.51 (2.41) | 7.64 (2.5) | F=23.98 (p<0.0001)
JOLO | 11.52 (0.77) | 11.52 (0.78) | 11.2 (1.26) | 11.03 (1.26) | F=12.49 (p=0.0059)
Letter-Number Sequencing | 13.23 (1.81) | 12.76 (2.40) | 12.87 (2.08) | 13.22 (2.49) | F=5.51 (p=0.1378)
Verbal Category Fluency | 11.03 (2.57) | 10.59 (2.29) | 10.63 (2.36) | 10.3 (2.44) | F=3.64 (p=0.0028)
Symbol-Digit Matching | 17.29 (3.84) | 17.08 (3.52) | 16.65 (3.69) | 15.03 (3.57) | F=15.67 (p=0.0013)

Early Parkinson’s Disease vs. Control-

Comparisons of Early Parkinson’s Disease

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<tr>
<th>Measure</th>
<th>ePD Aβ+ E-</th>
<th>ePD Aβ- E+</th>
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<td>Early Parkinson’s Disease vs. Control-</td>
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| Modified Schwab & England | 93.13 (5.83) | 91.36 (6.99) | U=7923 (p=0.0360)
| UPPS III | 20.83 (9.00) | 23.23 (9.01) | U=7282 (p=0.046)

Note: *Group-level comparison only between ePD+ and ePD-; **ePD+ vs. ePD- (p<0.005); ePD+ vs. ePD- (p<0.05); ePD+ vs. Control- (p<0.005); ePD+ vs. Control- (p<0.05); ePD+ vs. Control- (p<0.05); ePD+ vs. Control- (p<0.05); ePD+ vs. Control- (p<0.05); ePD+ vs. Control- (p<0.05); ePD+ vs. Control- (p<0.05); ePD+ vs. Control- (p<0.05); ePD+ vs. Control- (p<0.05).