PATHOLOGIC VALIDATION OF THE EADC-ADNI HARMONIZED HIPPOCAMPAL PROTOCOL

Liana Apostolova, Chris Zarow, Kristina Biado, Sona Hurtz, Marina Boccardi, Johanne Somme, Hedieh Honarpisheh, Anna Blanken, Jenny Brook, Spencer Tung, Denise Ng, Jeffrey Alger, Harry Vinters, Martina Bocchetta, Henry Duvernoy, Clifford Jack, Giovanni Frisoni

Background

The gold standard for Alzheimer's Disease (AD) diagnosis is post-mortem examination of brain tissue. Pathologic validation is the only definitive way to ascertain the validity of disease biomarkers. Hippocampal atrophy is the most established structural imaging biomarker for AD to date. European AD Consortium and AD Neuroimaging Initiative investigators recently developed a Harmonized Protocol for Hippocampal Segmentation (EADC-ADNI HarP). EADC-ADNI HarP has not yet been pathologically validated.

Methods

The temporal lobes of 9 AD and 7 cognitively normal subjects (NC) were scanned post-mortem at 7 Tesla. Pathologic diagnosis of AD was based on Braak and Braak and CERAD criteria. The temporal lobes were scanned for 60 hours on a 7T Bruker Biospec MRI scanner. Hippocampal volumes were obtained with the EADC-ADNI HarP. 6 µm-thick hippocampal slices were stained for amyloid beta (Aβ1-40), tau and cresyl violet. The demarcations of each hippocampal subfield were manually drawn with Aperio ImageScope® CS on the digitally scanned stained tissue. Subfield margins were identified based on cytoarchitectonic features. Neuronal counts, Aβ and tau burden for each hippocampal subfield were obtained.

Results

Kruskal-Wallis comparison of medians showed significant differences between the two groups for total hippocampal tau and Aβ burden (p=0.01 for both) but not neuronal count (p=0.12). Significant differences in the medians were also seen in all subfields for tau and in the subiculum, CA1 and CA3 for Aβ. We found significant correlations between hippocampal volume and fresh brain weight (ρ=0.69, p=0.003), Braak and Braak staging (ρ=-0.71, p=0.002), tau (ρ=-0.53, p=0.034) and Aβ burden (ρ=-0.61, p=0.012). Subfield-wise significant association were found for Aβ in CA1 (ρ=-0.58, p=0.019) and subiculum (ρ=-0.75, p=0.001), as well as tau in CA2 (ρ=-0.59, p=0.016) and CA3 (ρ=-0.5, p=0.047).

Conclusions

The observed associations provide pathologic validation for the EADC-ADNI HarP and pathologic confirmation of hippocampal morphometry as a valid AD biomarker.