Primary Age-Related Tauopathy and Successful Aging

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Introduction

Primary age-related tauopathy (PART) is a neuropathologic entity characterized by neurofibrillary degeneration that is primarily restricted to Braak stage I-IV, absent or sparse neocortical neuritic plaques and Thal amyloid phase 0-2. In symptomatic patients, clinical features generally consist of a milder amnestic type impairment and longer lifespan than Alzheimer Disease (AD) patients.

Abstract

We have previously demonstrated a selective vulnerability of the CA2 subregion of the hippocampus in PART for neurofibrillary degeneration. This is a distinguishing feature from AD that generally displays sparing of CA2 in early to intermediate stages (Figures 1-2). The objective of this study is to further analyze PART neuropathologic changes including the asymmetry of hippocampal neurofibrillary degeneration.

Materials and Methods

Here we assessed the regional distribution of abnormal tau burden in PART cases where bilateral hippocampi were available for analysis (n=59). These cases are from the PART Working Group Study (a multi-institutional study currently analyzing over 1000 PART cases to determine the unique genetic, biochemical and neuropathologic characteristics of this disorder). Tau pathology was analyzed using AT8 immunohistochemically stained sections of posterior hippocampus.

Results

We observed asymmetry of tau pathology in subregions of the hippocampus in 42% (25/59) of PART cases. These findings were confirmed in a supporting cohort from SUNY Upstate where asymmetry was identified in 61% (13/21) of PART cases. Comparisons of tau pathology in the entorhinal and each of the CA subregions of the right and left hippocampus revealed that the asymmetry was primarily focused in the CA2 subregion (Figures 3-4). Previous studies have reported asymmetry of tau pathology in 23-35% of AD cases and up to 90% of AGD cases (1.2). The CA2 neurofibrillary degeneration in PART cases is significantly greater than the CA1 neurofibrillary degeneration (Figure 3). In PART cases, the CA2 subregions that were analyzed exhibited CA2 neurofibrillary degeneration in 35% of PART cases (25/59). These findings were further characterized by the CA2/CA1 ratio of neurofibrillary degeneration when the hippocampus with the more severely affected CA2 is assessed (Figures 5-6). In conclusion, analyzing bilateral hippocampi is essential for the recognition of asymmetry of neurofibrillary degeneration in subregions of the hippocampus and could have clinical diagnostic implications in the future with advanced imaging and tau-PET. These findings could also further our understanding of resilience (where an individual with significant pathology displays minimal to no cognitive decline) given the possibility that there is less severe pathology in the hippocampus that was not analyzed, providing a potential source of cognitive reserve.

Conclusion

In conclusion, analyzing bilateral hippocampi is essential for the recognition of asymmetry of neurofibrillary degeneration in subregions of the hippocampus and could have clinical diagnostic implications in the future with advanced imaging and tau-PET. These findings could also further our understanding of resilience (where an individual with significant pathology displays minimal to no cognitive decline) given the possibility that there is less severe pathology in the hippocampus that was not analyzed, providing a potential source of cognitive reserve.

Future Directions

Genetic Analyses:
Deep sequencing has been performed on all of the PART cases in the PART Working Group Study. Our plans are to complete GWAS associating genetic variations with pure PART cases. However, these data lend themselves to many other potential projects.

References