Analysis of Spatio-Temporal Features of Histopathology in Murine AD Models and Human AD Samples

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BACKGROUND & AIMS

Alzheimer’s disease (AD) is a degenerative brain disease characterized by two pathological hallmarks: amyloid plaques and neurofibrillary tangles (NFTs). The latter consists of hyperphosphorylated protein tau. This protein is, under physiological conditions, responsible for the axonal microtubule stabilization. Hyperphosphorylated tau protein may aggregate and further lead to NFTs and the loss of the stabilizing function. The hyperphosphorylation takes place at certain tau protein residues like serine, threonin and tyrosine. This study was done to investigate tau pathologies in transgenic APP69 mice overexpressing the human APP and in human brains. The aim of this study is to test if there is an increase of tau with age or Braak stage, respectively. Furthermore, it will be examined if APP69 mice show any tau pathologies at all in the absence of human tau mutations. If murine tau protein aggregates in transgenic mice and can be evaluated the same way as in human samples, APP69 mice could be a potential model of human AD histopathology.

MATERIALS AND METHODS

Indirect immunofluorescence was used to visualize hyperphosphorylated tau for three specific phospho-sites (pSer199, pSer396, and pSer422) on human and mouse tissue, using:

- human demented brain samples (Braak I/II, III/IV, V/VI) and healthy controls, 5 brain areas
- Transgenic APP69 mouse brains (6, 9 and 12 months) and age-matched non-transgenic controls
- Polyclonal Rabbit Anti-Tau pSer199
- Monoclonal Mouse Anti-Tau pSer396 (clone PHF13)
- Monoclonal Mouse Anti-Tau pSer422 (clone 5.6.11)

RESULTS

pSer199, pSer396 and pSer422 increase with disease progression in human brains

pTau labeling in front cortex across Braak stages

Example of pSer422 labeling in cortex and HC

Quantification of pTau in human cortical areas and hippocampus

CONCLUSION

Data showed a comparable increase of pSer396 tau and pSer422 tau over age and Braak stage for APP69 mice and human samples, respectively. The results of pSer199 tau showed a decrease over age, while in human tissues an increase over Braak stages occurred. The APP69 mouse model is in some read-outs similar to human samples. The APP69 mouse is therefore a useful model for the analyses of tau-related AD pathologies.