Title

Early neuropathological lesions in late-onset Alzheimer's disease



Journal

ANNALS OF NEUROLOGY, 42(3)

ISSN

0364-5134

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Publication Date

1997-09-01

## DEMENTIA AND AGING

### M15. Early Neuropathological Lesions in Late-Onset Alzheimer's Disease

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We examined for markers of Alzheimer's disease (AD) and for abnormalities of the endosomal/lysosomal system the brains of a 74-year-old woman with AD (apolipoprotein E [APoE], 4/4; Mini-Mental State Examination score, 14) and of her 47-year-old nondemented daughter (ApoE, 2/4). The brain of the mother showed widespread neuritic senile plaques and neurofibrillary tangles, confirming the diagnosis of AD. The senile plaques immunostained for Aβ-amyloid and were associated with microglia (HLA-DR–positive) and astrocytes (GAFP-positive). The brain of the daughter showed abundant cortical deposits of diffuse Aβ surrounding normal-appearing neurons. These Aβ deposits were not associated with neuritic abnormalities or microglial or glial reaction. Furthermore, there were no neurofibrillary tangles in the cortex or hippocampus. Most pyramidal neurons in the prefrontal and temporal cortices of both subjects revealed strikingly large rab-5–positive endosomal profiles compared with controls and a marked increase in cathepsin D–positive late endosomes and lysosomes. These observations suggest that the early pathological changes in late-onset familial AD are perineuronal deposits of diffuse Aβ accompanying endosomal and lysosomal abnormalities that precede clinical onset by decades. Furthermore, Aβ deposits precede overt neurofibrillary changes.

Study supported by Johns Hopkins ADRC-AG05146.