SUNDAY, JULY 13, 2014
SYMPOSIA
S1-01
IS IT ONLY ALZHEIMER'S DISEASE, AND IS THAT IMPORTANT?

S1-01-01 PATHOLOGY UNDERLYING REGIONAL BRAIN ATROPHY

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Background: To examine the association between longitudinal changes in total and regional brain volumes and pathology. **Methods:** Research participants of the Oregon Alzheimer's Disease Center were followed on average for 7 years with annual MRI scans until death. Initial MRI was obtained before onset of dementia and last MRI within a mean of 15 months of death. Average age at death was 95 years. Using mixed-effects models the relationship between longitudinal changes in regional brain volumes (ventricular, total brain, and hippocampal) and pathology (neurofibrillary tangles (NFTs), neuritic plaques (NPs), gross infarcts, microinfarcts, amyloid angiopathy, Lewy Bodies) was examined adjusting for APOE status, diagnosis, duration of follow up and age at death. In a subset of participants the relationship between white matter hyperintensity (WMH) accumulation and pathology (myelin pallor, arteriolosclerosis, atherosclerosis, microvascular disease, microinfarcts, large vessel infarcts, lacunar infarcts, amyloid angiopathy, NFTs and NPs) was examined using a similar statistical approach. **Results:** Ventricular enlargement over time was associated with infarcts ($p<.001$), NFTs ($p=.015$), NPs ($p=.001$), age ($p<.001$), and presence of the ε4 allele ($p<.001$). Ventricular enlargement accelerated in mild cognitive impairment (MCI) ($p=.04$) and dementia ($p<.001$) compared to normal cognition. Total brain atrophy was associated with age ($p<.001$), amyloid angiopathy ($p=.03$) and infarcts ($p=.04$) and also accelerated in MCI ($p=.004$) and dementia ($p=.02$). Longitudinal hippocampal atrophy was only associated with amyloid angiopathy ($p=.009$). WMH accrual was associated with arteriolosclerosis ($p<.0001$), myelin pallor ($p=.04$), NFTs ($p=.008$) and presence of the ε4 allele ($p=.02$). In post-hoc analysis, those with highest NFT burden had significantly more atherosclerosis compared to those with lowest NFT burden. **Conclusions:** Ventricular volume trajectory is more sensitive than total brain and hippocampal atrophy as a marker of accruing Alzheimer's and cerebrovascular disease pathology in the oldest old. Because MCI and dementia diagnosis contributed to more brain atrophy despite adjusting for pathology, other unmeasured factors are likely contributing to brain atrophy. Last, while arteriolosclerosis is the main driver of WMH accumulation, the observed association between NFTs and WMH accumulation supports a link between cerebrovascular disease and Alzheimer's disease.

S1-01-02 HIPPOCAMPAL SCLEROSIS PATHOLOGY IN THE OLD AND OLDEST-OLD LIVING IN THE COMMUNITY

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Background: There is increasing recognition of hippocampal sclerosis (HS) pathology in older persons. Yet, there is little data on HS in the old and oldest old living in the community. Objectives: We investigated the role of HS pathology in dementia, clinical Alzheimer's disease (AD), and specific domains of cognitive impairment in deceased old and oldest-old who had been living in the community. **Methods:** The study included 1052 autopsied subjects (632 <90 and 420 $\geq$ 90 years) from the Rush Religious Order Study (n=569) and the Memory and Aging Project (n=483), longitudinal community-based clinical-pathological studies. Dementia was based on review of clinical evaluation and cognitive performance tests, and the latter were used to create a measure of global cognition and of five cognitive domains proximate to death. HS was considered present if there was severe neuronal loss and gliosis in the hippocampus CA1 and/or subiculum. Statistics included multiple regression analyses. **Results:** HS was present in 84 subjects (8%); 12.1% of oldest-old and 5.2% of old. 66 (78.6%) subjects with HS had a pathologic diagnosis of AD; 27 (32.1%) had lewy bodies (LB), 35 (41.7%) had macro-infarcts, and 30 (35.7%) had microinfarcts. After controlling for age, sex, and education, and other pathologies, AD ($p<0.001$) and LB pathologies ($p=0.01$) were independently associated with HS. There were more infarcts in persons with HS compared those without, but this did not reach statistical significance. Similarly, neither atherosclerosis nor arteriolosclerosis increased the odds of HS. After controlling for demographics and other pathologies, HS was related to increased odds of dementia (OR=4.6; 95% CI=2.34-9.97) specifically, and clinically probable AD (OR=5.75; 95% CI=2.82-11.73). As expected, HS was associated with lower episodic memory, however it was also associated with lower function in language, visuospatial skills, and perceptual speed, proximate to death. Effects were not modified by age. **Conclusions:** HS in aging is most common in the oldest old, often but not always related to AD or LB pathologies, and is independently associated with increased likelihood of dementia, specifically probable AD. HS is associated with impaired function in episodic memory, language, visuospatial skills, and perceptual speed suggesting HS is a widespread brain disease.

S1-01-03 CEREBRAL AMYLOID ANGIOPATHY AND ALZHEIMER'S DISEASE

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Background: Deposition of ß-amyloid peptide in the cerebral arterioles, small arteries, and capillaries, designated as cerebral amyloid angiopathy (CAA), is a nearly universal accompanying feature of Alzheimer's Disease (AD). Mild CAA appears to have little effect on vessels, but more advanced stages are associated with vascular rupture and intracerebral hemorrhage as well as with impaired vascular function, nonhemorrhagic brain lesions, and cognitive impairment. The Religious Orders Study, for example, demonstrated worse perceptual speed and episodic memory-independent of AD pathology and other covariates-among the one-fifth of individuals with moderate-to-very severe CAA. These findings suggest that AD and CAA might frequently act in concert to produce mixed dementia. A second link between AD and CAA are the striking similarities between the vasogenic edema-amyloid related imaging abnormalities (ARIA-E) seen in AD immunotherapy trials and the spontaneous syndrome of CAA-related inflammation. CAA-related inflammation appears to be driven by cerebrospinal production of anti-amyloid autoantibodies, indicating a shared mechanism for the two syndromes. Despite concerns about antibody-mediated adverse events, the key pathogenic role of ß-amyloid in CAA makes anti-amyloid immunotherapy a rational therapeutic approach for this largely untreatable disease.

S1-01-04 OVERLAPPING PROTEINOPATHIES IN THE ELDERLY AND THEIR SIGNIFICANCE

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Background: Neurodegenerative diseases of the elderly are characterised by neuronal loss and cerebral deposition of proteins with altered physicochemical properties. The major proteins are amyloid-β (Aβ), tau, α-synuclein, and TDP-43. Although neuropathological studies on elderly individuals have emphasized the importance of mixed pathologies, there have been few observations on the full spectrum of proteinopathies in the ageing human brain. **Methods:** During a community-based study (Vienna Trans-Danube Aging; VITA) study) we performed comprehensive mapping of neurodegeneration-related proteins and vascular pathology in the brains of 233 individuals (age at death 77-87). We applied immunostaining for neurodegeneration-related proteins in several anatomical regions. Logistic regression models were used to assess the univariate and multivariable effect of pathological variables.