Brain Reserve is as Important as Alzheimer and Vascular Pathology in Determining Dementia Status: The Nun Study

James A Mortimer[1], Amy R. Borenstein[1], [1]*University of South Florida, Tampa, Florida, United States.*

Background: Although Alzheimer and vascular pathology are known to be strong determinants of dementia, the relative importance of brain reserve (brain volume and education) in affecting dementia status is unknown. **Methods:** Using data from the Nun Study, we calculated etiologic fractions for predictors of dementia at death. Predictors were determined from a factor analysis of known risk factors including educational attainment, presence of one or more apolipoprotein E-epsilon4 alleles, as well as mean densities of neurofibrillary tangles and neuritic plaques in the neocortex, presence of lacunar and large infarcts, rating of arteriosclerosis in the circle of Willis, and brain weight (excluding meninges) determined at autopsy. **Results:** Three factors with Eigenvalues from 1.24-1.73 were identified [loadings indicated by L]: (1) Alzheimer's pathology (tangle [L= .82] and plaque counts [L=.75], and APOE4 [L=.65]); vascular pathology (atherosclerosis [L=.60], lacunar [L=.78] and large infarcts [L=.70]); and reserve (education [L=.79], brain weight [L=.73]). Factor scores were calculated and dichotomized at the median to yield high and low values for each factor. Etiologic fractions (fraction of cases attributable to each of the risk factors) for high Alzheimer, high vascular and low reserve were 38.5%, 25.6% and 39.7%, respectively. In other analyses, we found that brain weight at autopsy was most strongly related to head circumference ($p<0.0001$) rather than to Alzheimer ($p=0.01$) or vascular ($p=0.67$) pathology, suggesting that early brain growth plays a more important role in determining brain weight at death than brain pathology. **Conclusions:** Brain reserve plays a very strong role in determining dementia status at death, on a par with Alzheimer pathology. Higher reserve may help to explain the absence of dementia in about a third of individuals fulfilling Reagan criteria for neuropathological AD. Models predicting lifetime risk of AD need to take into account reserve and vascular lesions in addition to beta amyloid load. The findings suggest that interventions that facilitate brain growth may be very effective in preventing dementia.