Increase in Caudate Size with Age in Carriers of the A431E *PSEN1* Mutation

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Abstract

Background: Persons at-risk for inheriting fully-penetrant autosomal dominant forms of Alzheimer's disease (familial AD or FAD) provide a unique opportunity to identify imaging changes occurring early in the presymptomatic phase of the illness. However, there are clinical and pathological differences between FAD and late-onset AD as well as among FAD pedigrees with diverse FAD mutations. Families with *PSEN1*-related FAD, due to the A431E substitution, sometimes demonstrate spastic paraparesis and "cotton-wool" plaques (CWPs) on pathological examination. In the current study we sought to quantify changes in caudate size and cortical thickness with age in presymptomatic carriers of this mutation.

Methods: Fourteen non-demented (CDR scores less than 1) A431E PSEN1 mutation carriers underwent volumetric MRI scans on the same scanner using a standard high-resolution 3D MPRAGE sequence. Cortical thickness was computed from gray matter segmentations at each point of a 3D cortical surface model extracted for each subject. Caudate volumes were manually delineated in ICBM space using FSL. Right and left caudate volumes were averaged within subjects. Mean hemispheric cortical thickness was computed. All measurements were performed by persons blind to all clinical information including mutation status. As age of disease onset tends to be consistent within families, subjects' age relative to the median age of dementia diagnosis was calculated and correlations sought between relative age and cortical thickness and caudate volumes.

Results: Among non-demented A431E mutation carriers, average caudate volume was positively correlated with relative age ($r = 0.55$, $p = 0.04$). Mean cortical thickness showed a significant negative correlation with relative age in this population (left hemisphere $r=-0.59$, $p<0.0001$; right hemisphere $r=-0.61$, $p<0.0001$).

Conclusions: Caudate volumes appear to increase while cortical thickness appears to decrease with age in pre-clinical carriers of the A431E PSEN1 mutation. Though the reason for the observed effect in the caudate is not entirely clear, one possible explanation is the CWPs are "space occupying" in the caudate and therefore increase caudate volume prior to the development of overt dementia. This has important implications when considering volumetric measures as markers of disease status or progression.