ASSOCIATION BETWEEN THE APOLIPOPROTEIN E &[EPSILON]4 GENE POLYMORPHISM AND CEREBRAL VENTRICULAR DILATATION MEASURED FROM SERIAL MAGNETIC RESONANCE IMAGING IN SUBJECTS ENROLLED IN THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

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Introduction: The allele ε4 of the gene apolipoprotein ε (*APOE*) has been implicated as a genetic risk factor in Alzheimer disease [1]. Structural MRI measures of whole brain changes and medial temporal lobe atrophy have been previously associated with polymorphisms at the *APOE* locus in subjects with Alzheimer disease and mild cognitive impairment [2]. Genotypic associations with measures of cerebral ventricular dilatation, a sensitive surrogate measure of cerebral atrophy, have been less well characterized, particularly over intervals of <1 year, in subjects with MCI and AD. The purpose of the current study is to quantify ventricular dilatation in both carriers for the ε4 allele (ε4+) and subjects with either ε2 and/or ε3 alleles (ε4-), over an interval of six-months from baseline. We hypothesize that the ε4+ AD subjects will have greater ventricular dilatation than ε4- AD subjects, and we expect a similar trend in patients with MCI.

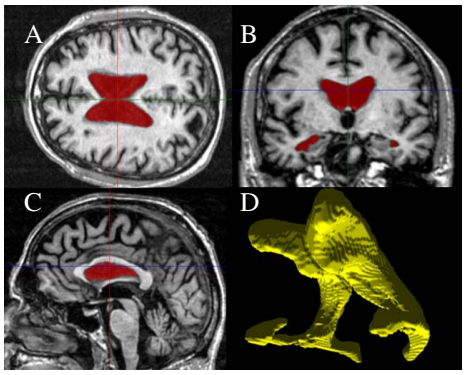

Figure 1: (A) Axial, (B) Coronal, (C) Sagittal planes with lateral ventricle depicted red, (D) screen shot of 3D rendered ventricle

Methods: Six-month longitudinal data were selected from the ADNI database [3], which included one-hundred-fifty normal elderly controls (NEC) (mean age=76 years), two-hundred-forty-seven subjects with MCI (mean age = 76 years) and one-hundred-five subjects with AD (mean age = 76 years). Baseline and six-month unprocessed 3D T_1-weighted MP-RAGE MR images (1.5 Tesla General Electric MR scanners were used, TR = 8.91 ms, TE =3.92 ms, TI = 1000 ms, field-of-view = 24 cm, in-plane matrix size = 256 x 256, slice thickness = 1.2 mm, and 1.5 Tesla Siemens MR Scanners were also used) and corresponding neurocognitive, demographic and genetic measures were acquired. Ventricular volume was computed using a semi-automated region-growing algorithm (Cedara Software, Mississauga, Ontario, Canada), with a quality control application. Baseline and repeat images were not registered prior to analysis, and all analyses were completed blind to subject group, phenotype, and time of scan. Subjects within all groups were dichotomized into ε4- (ε2/ε3 heterozygote or ε2/ε3 homozygote) and ε4+ subjects (ε4 homozygote or ε4 heterozygote). Pearson correlations were employed to test for relationships between neurocognitive and volumetric measures. Independent samples t-tests were used for comparisons between APOE polymorphic groups.

Results: Approximately 70 percent of AD subjects and 50 percent of MCI subjects were ε4+. Ventricular dilatation was significantly greater in the AD ε4+ group compared to AD ε4- subjects ($p< 0.05$) (Fig.2). However, there were no differences realized in either the MCI or NEC genotypic groups. There were no differences between genotypic groups on either the Alzheimer Disease Assessment – cognitive subscale (ADAS-cog) or the Mini Mental State Exam (MMSE). Modest correlations were demonstrated between changes in both ADAS-cog scores ($r = 0.153$, $p< 0.05$) and MMSE scores ($r = 0.188$, $p< 0.01$) when associated with ventricular dilatation in subjects with MCI.

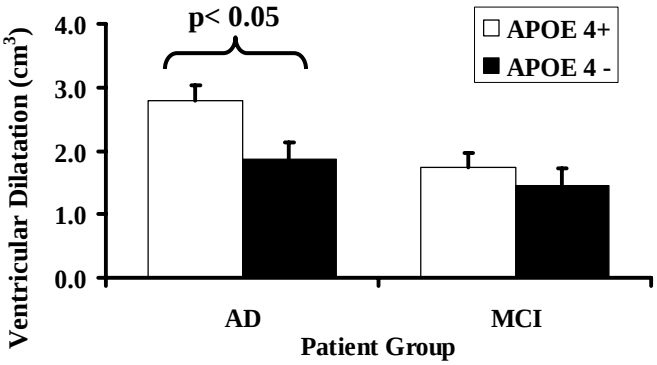

Figure 2: Comparison of mean ventricular dilatation after six months, pathological groups are dichotomized for genotype (error bars represent standard error)

Conclusion: Ventricular dilatation measured after only six-months demonstrates marked interval progression in AD ε4+ carriers. Applied as a surrogate biomarker of tissue atrophy, ventricular dilatation provides insight into the pathological phenotype of AD and differential disease progression in the absence of detectable neurocognitive differences.

References:

[1] Martinez, M., *et al*. Apolipoprotein E ε4 allele and familial aggregation of Alzheimer disease. *Arch. Neurol* 1998; 155: 779-784.

[2] Bigler, E.D., e*t al*. Dementia, quantitative neuroimaging, and apolipoprotein E genotype. *Am J Neuroradiol* 21: 1857-1868.

[3] http://www.loni.ucla.edu/ADNI/Data/