Role of Family History for Alzheimer Biomarker Abnormalities in the Adult Children Study

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Objective: To assess whether family history (FH) of Alzheimer disease (AD) alone influences AD biomarker abnormalities.

Design: Adult Children Study.

Setting: Washington University’s Charles F. and Joanne Knight Alzheimer’s Disease Research Center.

Participants: A total of 269 cognitively normal middle-to older-aged individuals with and without an FH for AD.

Main Outcome Measures: Clinical and cognitive measures, magnetic resonance imaging–based brain volumes, diffusion tensor imaging–based white matter microstructure, cerebrospinal fluid biomarkers, and molecular imaging of cerebral fibrillar amyloid with positron emission tomography using the [11C] benzothiazole tracer, Pittsburgh compound B.

Results: A positive FH for AD was associated with an age-related decrease of cerebrospinal fluid Aβ42; the ε4 allele of apolipoprotein E (APOE4) did not alter this effect. Age-adjusted cerebrospinal fluid Aβ42 was decreased for individuals with APOE4 compared with the level for those without, and the decrease was larger for individuals with a positive FH compared with the decrease for those without. The variation of cerebrospinal fluid tau and Pittsburgh compound B mean cortical binding potential increased by age. For individuals younger than 55, an age-related increase in mean cortical binding potential was associated with APOE4 but not FH. For individuals older than 55, a positive FH and a positive APOE4 implied the fastest age-related increase in mean cortical binding potential. A positive FH was associated with decreased fractional anisotropy from diffusion tensor imaging in the genu and splenium of the corpus callosum.

Conclusion: Independent of APOE4, FH is associated with age-related change of several cerebrospinal fluid, Pittsburgh compound B, and diffusion tensor imaging biomarkers in cognitively normal middle- to older-aged individuals, suggesting that non-APOE susceptibility genes for AD influence AD biomarkers.

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Recent advances suggest that Alzheimer disease (AD) has a lengthy period in which cerebral lesions gradually accumulate in the absence of symptoms, eventually causing sufficient synaptic and neuronal damage to result in symptomatic AD. Since 2005, Antecedent Biomarkers for AD: The Adult Children Study (ACS) has enrolled a cohort of cognitively normal 43- to 76-year-old individuals in an extensive study of biomarkers for AD before its symptomatic stages. In addition to clinical and cognitive measures, a broad spectrum of candidate antecedent biomarkers for AD were assessed, including magnetic resonance imaging (MRI)–based brain volumes, diffusion tensor imaging–based measures of white matter microstructure, cerebrospinal fluid (CSF), and molecular imaging of cerebral fibrillar amyloid with positron emission tomography (PET) using the [11C] benzothiazole tracer, Pittsburgh compound B (PIB). Because the ACS cohort is cognitively normal, changes in these well-established biomarkers for AD likely represent the insidious pathogenesis of AD well before the development of symptoms, ie, during the preclinical stage of AD.

The ACS cohort is stratified by family history (FH) for AD to genetically enrich the participants at risk of AD. Therefore, analysis on FH and biomarkers allows a linkage of biomarker abnormality to susceptibility genes for AD, especially non-apolipoprotein E (APOE) genes (ie, PICALM, CR1, and CLU discovered from recent genome-wide association studies) if the effect of FH is independent of APOE. Whereas several studies reported changes in isolated biomarkers with rela-
tively small samples of elderly normal individuals with an FH of AD8-10 or the e4 allele of APOE (APOE4) (OMIM +107741).11 The ACS facilitates a comprehensive analysis of both FH and APOE for a wide array of candidate antecedent biomarkers in cognitively normal individuals of middle to older age (43-76 years).

The objective of this study was to assess whether FH alone conveys AD risk beyond that of APOE4 by examining the influence of FH for AD, both together and independent of APOE4, on biomarker abnormalities using the baseline data of the ACS.

**METHODS**

**PARTICIPANTS**

As of October 2009, the ACS cohort included 269 community-living volunteers from the greater St Louis metropolitan area. Recruitment primarily was through word of mouth and personal inquiries. A positive FH for AD was defined as at least 1 biological parent with age at onset for dementia of the Alzheimer type (DAT) of less than 80 years, and a negative FH was defined as both biological parents living to age 70 or longer without DAT. If a parent living to age 70 without DAT later developed DAT by age 80, the participant was reassigned to the positive FH group. About one-third of the participants were children of parents enrolled in longitudinal studies of the Washington University Alzheimer’s Disease Research Center. Eligibility criteria for the ACS were age 45 to 75 (2 early enrollees were age 43 and 76 years), availability of an informant who knew the participant well, normal cognition (defined as Clinical Dementia Rating12 of 0), and willingness in principle to complete all procedures. Comorbid conditions, including depressive features short of major affective disorder, were acceptable if the patient was clinically stable at time of enrollment. Exclusion criteria included conditions such as end-stage cancer or end-stage renal disease that would preclude longitudinal participation and/or confound cognitive assessment. Another exclusion criterion was membership in families with a dominantly inherited pattern of AD and/or a known causative mutation for AD. The Washington University Human Research Protection Office approved the study.

**CLINICAL AND COGNITIVE ASSESSMENTS**

The primary clinical assessment protocol was that of the National Alzheimer Coordinating Center Uniform Data Set.13 Additional clinical information, such as an assessment of autobiographical memory using events in which the participant well, normal cognition (defined as Clinical Dementia Rating12 of 0), and willingness in principle to complete all procedures. Comorbid conditions, including depressive features short of major affective disorder, were acceptable if the patient was clinically stable at time of enrollment. Exclusion criteria included conditions such as end-stage cancer or end-stage renal disease that would preclude longitudinal participation and/or confound cognitive assessment. Another exclusion criterion was membership in families with a dominantly inherited pattern of AD and/or a known causative mutation for AD. The Washington University Human Research Protection Office approved the study.

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**CSF COLLECTION AND ANALYSIS**

Cerebrospinal fluid (20-30 mL) was collected by routine lumbar puncture, free from any blood contamination, in polypropylene tubes at 8:00 AM after overnight fasting, as previously described.14 The samples were analyzed for total tau, tau phosphorylated at threonine-181 (ptau181), and Aβ1-42 by commercial enzyme-linked immunosorbent assay (Innotest; Innogenetics, Ghent, Belgium). Cerebrospinal fluid Aβ40 was assayed by enzyme-linked immunosorbent assay as previously described.30 For all CSF measures, samples were continuously kept on ice, and assays were performed on sample aliquots after a single thaw following initial freezing.

**IMAGE ACQUISITION AND PROCESSING**

Magnetic resonance imaging scans were obtained on either a Sonata 1.5T, Vision 1.5T, or Trio 3.0T scanner (Siemens Corporation, Malvern, Pennsylvania). Structural MRI processing steps have been described in detail previously28-30 and include motion correction, averaging across scans, atlas transformation, and inhomogeneity correction. Regional volumes were obtained via the Freesurfer image analysis suite, version 4.1.0 (Athens, Georgia). The regions of interest are detailed elsewhere.37 A comparison between the Vision 1.5T and Trio 3.0T scanners of Freesurfer-derived volumes yielded an average intraclass correlation of 0.81.37 Analysis was performed on adjusted volumetric measures afterregressing for the effect of scanner platform.

Diffusion tensor images were collected at 3T for the assessment of white matter microstructural integrity (2x2x2-mm voxels, repetition time=9900 ms, echo time=102 ms, flip angle=90°, and b-values scaled up to 1400 maximum, using 23 diffusion encoding directions). Data were collected in two 6-minute runs. Quantitative images of mean diffusivity, fractional anisotropy, and axial and radial diffusivity for regions of interest were computed as previously described.30 Positron emission tomography PIB imaging and analysis procedures have been reported elsewhere.48 Brain PET imaging was conducted using a Siemens 961 HR ECAT PET scanner or a Siemens 962 HR+ ECAT PET scanner (both, Control Technology, Inc, Knoxville, Kentucky). Radiochemical synthesis of [11C]PIB was performed in accordance with the published literature.41 After a transmission scan to measure attenuation, approximately 12 mCi of [11C]PIB was administered intravenously simultaneously with initiation of a 60-minute dynamic PET scan in 3-dimensional mode (septa retracted; twenty-four 5-second frames, nine 20-second frames, and ten 1-minute frames). The measured attenuation factors, scatter correction, and a ramp filter were used to reconstruct the dynamic PET images. Analysis of PIB images was performed for specific regions of interest as detailed pre-
The dissociation task. The 2 span tasks involved participants making a series of true/false judgments, with the working memory component being to remember in order the parts of the stimulus across the judgments. The Stroop is a computerized color naming task, which includes 60 trials for the congruent (eg, BLUE in BLUE), neutral (eg, DEEP in BLUE), and incongruent (eg, RED in BLUE) conditions. The process dissociation task places recollection in direct conflict with familiarity via opposition procedures during retrieval. A Consonant–Vowel/Odd–Even Switching task was also administered.

ATTENTIONAL ASSESSMENT

A 2-hour attentional battery was administered separately from the psychometric testing. The attentional control tasks were computation span, letter rotation span, and a process dissociation task. The 2 span tasks involved participants making a series of true/false judgments, with the working memory component being to remember in order the parts of the stimulus across the judgments. The Stroop is a computerized color naming task, which includes 60 trials for the congruent (eg, BLUE in BLUE), neutral (eg, DEEP in BLUE), and incongruent (eg, RED in BLUE) conditions. The process dissociation task places recollection in direct conflict with familiarity via opposition procedures during retrieval. A Consonant–Vowel/Odd–Even Switching task was also administered.

GENOTYPING

We extracted DNA from peripheral blood samples using standard procedures. Apolipoprotein E genotyping was performed as previously described.

STATISTICAL ANALYSIS

The analysis was done on ACS baseline data. Each marker was analyzed as a function of age, FH (yes or no), and APOE4 genotype (ε4 allele present or absent) by the analysis of covariance. The interactive effects among these 3 risk factors were first tested and reported if confirmed. Otherwise, independent effects of each risk factor were reported. Preliminary analysis suggested differential variances as a function of age (ie, younger vs older than 55), which were tested and then accommodated in the associational analyses with FH and APOE4 if confirmed. The software PROC MIXED/SAS was used to implement these analyses. The Satterthwaite approximation was used to estimate the denominator df in the approximate F or t tests.

Table 1 presents the demographic characteristics of the entire sample and subgroups with each modality of assessments. All 269 participants completed baseline clinical and psychometric assessments. Two hundred seventeen participants (80.7%) had a lumbar puncture to obtain CSF, 206 (76.6%) completed PET PIB, 147 (54.6%) had an MRI, and 232 (86.2%) completed the attentional battery. One hundred eight participants (40.1%) completed all baseline procedures (clinical, psychometric, attention, lumbar puncture, MRI, and PET PIB).

As shown in the Figure, the mean (SE) level of CSF Aβ42 decreased significantly with age at a rate of −7.76 (2.14) pg/mL per year (P < .001) in those with a positive FH but not in those without (P = .35). The presence of an APOE4 allele did not alter the effect of FH on the age-related decrease in CSF Aβ42 (P = .50). Those with an ε4 allele had lower levels of age-adjusted CSF Aβ42 compared with the corresponding level in those without (P < .001), and the decrease was larger if FH was positive compared with the decrease if FH was negative (F1,209 = 5.29, P = .02). Sensitivity analyses with multiple imputations on CSF Aβ42 confirmed these findings.
The variance increased among individuals aged 55 or older compared with that of the younger age group for CSF tau ($\chi^2=9.71; P=.002$) and MCBP ($\chi^2=98.35; P<.001$). Table 2 presents the estimated slope (per year of age) for MCBP and CSF tau on younger (<55 years) and older individuals (≥55 years) as a function of FH and APOE4. No significant effect of FH or APOE4 was found for CSF tau on the age-related rate of change, but individuals with a positive FH had a higher level of CSF tau than those otherwise ($F_{1,152}=5.06; P=0.03$) at age 55. For individuals younger than 55, MCBP increased by age at a significantly faster pace for individuals with APOE4 compared with the pace for those without APOE4 ($F_{1,62}=4.72; P=.03$), eventually leading to a higher level of MCBP for those with APOE4 compared with the level for those without ($P=.01$). For individuals older than 55, a trend ($P=.09$) was found to suggest a faster age-related increase of MCBP for individuals with APOE4 compared with the increase for those without APOE4. Individuals with a positive FH and a positive APOE4 had the largest age-related increase of MCBP ($P<.001$).

Brain volumes as determined by MRI decreased with age, but the difference was not statistically significant by FH (total cerebral brain volume: $F_{1,136}=0.90; P=.34$; right hippocampal volume: $F_{1,136}=1.85; P=.18$; left hippocampal volume: $F_{1,136}=0.31; P=.58$).

From a subsample of 165 participants who had diffusion tensor imaging data, the age-adjusted mean level of fractional anisotropy was lower for individuals with an FH of AD compared with the level for those without an FH of AD in the genu ($F_{1,142}=3.91; P=.05$) and in the splenium ($F_{1,142}=4.12; P=.04$) of the corpus callosum. In the gyrus rectus, individuals with APOE4 had a lower level of fractional anisotropy ($F_{1,142}=4.75; P=.03$) and a higher level of radial diffusivity ($F_{1,142}=4.3; P=.04$) than those without APOE4. The age-related increase in radial diffusivity in the precuneus was faster if FH was positive, compared with the increase if FH was negative, only among individuals with APOE4 ($F_{1,142}=4.67; P=.03$). The mean (SE) performance level of auditory consonant trigrams decreased significantly with age at the rate of −0.411 (0.125) per year ($P=.001$) for those with a positive FH but not for those with a negative FH ($P=.52$).

One hundred fifteen and 52 participants reported their mother’s and their father’s age of onset of DAT, respectively. An earlier mother’s age of onset was correlated with a larger reaction time difference between pure blocks and switched blocks of trials from the Consonant–Vowel/Odd–Even Switching task$^{46}$ (Spearman $r=−0.21; P=.04$), and an earlier father’s age of onset was correlated with poorer performance in Wechsler Adult Intelligence Scale–III Similarities ($r=0.44; P=.01$).

Exploratory correlational analyses across the entire modalities of biomarkers confirmed those previously reported in the literature.$^{39,52,53}$ Significant correlations between MCBP and CSF biomarkers (tau $r=0.22$, ptau$^{181} r=0.19$, and CSF Aβ$42 r=−0.41$) were observed in the entire ACS cohort. Some of these are potentially modulated by age but not by FH. In the younger cohort (age <55 years), MCBP was not significantly correlated with CSF biomarkers or brain volumes. In the older cohort (age ≥55 years), however, MCBP was significantly correlated with CSF biomarkers (tau $r=0.24$, ptau$^{181} r=0.22$, and Aβ$42 r=−0.53$). Furthermore, CSF and imaging biomarkers were correlated with Stroop performance in the younger sample in only 2 occasions (Aβ$42$ with greater interference in reaction times $r=−0.28$, and MCBP with Simon coefficient of variation $r=0.31$). In the older sample, however, CSF and imaging biomarkers were correlated with poorer performance across many attention measures (eg, Aβ$42$ with task switching coefficient of variation $r=−0.22$ and interference errors $r=−0.20$; MCBP with task switching coefficient of variation $r=0.19$, interference RT $r=0.17$ and errors $r=0.19$, incongruent errors $r=0.19$, and Simon coefficient of variation $r=0.17$). Brain volumetric measures were also correlated with attentional and working memory measures (eg, total cerebral brain volume with rotation span $r=0.22$, and left hippocampal volume with rotation span $r=0.33$) in the older sample. Because of a large number of correlations assessed across all modalities of markers, these findings were subject to a higher false-positive rate (>5%). Therefore, they were preliminary and will serve only to generate scientific hypotheses that need to be critically tested in future studies.

Analyses were repeated on the subgroup of individuals who completed all procedures. The findings were con-
Family history for AD as a risk factor for AD and cognitive decline has been well documented, many times jointly with APOE4 genotypes. Several studies reported reduced gray matter volume and brain glucose metabolism as well as increased semantic memory activation in healthy individuals with a maternal history of AD. These reports, however, focused mostly on a small number of biomarkers assessed on the elderly population aged 65 or older. We reported the influence of FH for AD for a wide array of candidate antecedent biomarkers in the ACS cohort of cognitively normal middle- to older-aged individuals (aged 43-76 years). In addition to clinical and cognitive measures, we analyzed MRI-based brain volumes, diffusion tensor imaging–based estimates of white matter microstructure, biofluid assays, and molecular imaging of fibrillar amyloid measure with PET PIB.

No difference was found on cognitive and clinical measures as a function of FH of AD among cognitively normal ACS individuals. The only possible exception comes from the performance on the auditory consonant trigrams, and the difference is no longer significant after multiplicity adjustment.

Family history for AD, however, was associated with several CSF and imaging biomarkers in the cognitively normal ACS cohort, suggesting their potential role as antecedent biomarkers of AD. These findings support the design of the ACS that genetically enriched the sample of cognitively normal individuals at risk of AD by FH and are consistent with a recently reported meta-analysis of diffusion tensor imaging. The current results point to the likelihood of non-APOE susceptibility genes for AD, consistent with recent reports of multiple risk genes (PICALM, CR1, and CLU) of AD from several genome-wide association studies.

Together, our data across a wide spectrum of biomarkers on a cohort of cognitively normal middle- to older-aged individuals, albeit cross-sectional, suggest that AD has a lengthy period during which cerebral lesions gradually accumulate in the absence of symptoms (ie, preclinical AD). We expect that eventually these lesions cause sufficient synaptic and neuronal damage to result in symptomatic AD. More specifically, among cognitively normal middle- to older-aged individuals, age-related changes in brain Aβ42 metabolism as well as local microstructural characteristics of water diffusion in certain brain regions are influenced by FH of AD, suggesting that they are likely early events in AD pathogenesis. Significant disruptions in CSF tau and ptau181 metabolism, reflecting other changes in the structural integrity of axonal tracts, likely occur after brain Aβ42 initially aggregates and then increases as amyloid accumulates. Interestingly, CSF Aβ42 and MCBP are correlated with several of the attentional measures. These correlations suggest that antecedent biomarker changes likely have a deleterious effect on neuronal and attentional integrity.

For CSF tau and MCBP, we also observed increased variability as a function of age, which was further accompanied by an accelerated age-related increase. This finding, although cross-sectional, is consistent with several longitudinal studies in which an accelerated cognitive decline preceding the onset of DAT was reported. Whereas cognitive changes might be later events in the neurodegenerative sequence before the onset of DAT, changes in CSF and PIB biomarkers have the potential to capture the earliest possible antecedent events. This study has several limitations. First, the ACS is an observational study on a convenience sample. Unobserved factors could contribute to the differences of subgroups with each modality of measures. The interpretation of the findings thus has the standard limitations of observational studies. Second, a lack of longitudinal data on biomarkers prevents us from understanding the cascade of early events in AD pathogenesis. The ongoing longitudinal follow-up of clinical and biomarker measures on the ACS cohort will provide much more insight into the preclinical progression of AD.

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Author Contributions: Dr Xiong had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Xiong, Roe, Buckles, Mintun, Csernansky, and Morris. Acquisition of data: Fagan, Balota, Duchek, Storandt, Mintun, Grant, Head, Benzinger, Mettenburg, and Morris. Analysis and interpretation of data: Xiong, Roe, Buckles, Holtzman, Duchek, Snyder, Benzinger, and Morris. Drafting of the manuscript: Xiong, Balota, and Snyder. Critical revision of the manuscript for important intellectual content: Xiong, Roe, Buckles, Fagan, Holtzman, Duchek, Storandt, Mintun, Grant, Head, Benzinger, Mettenburg, Csernansky, and Morris. Statistical analysis: Xiong, Roe, and Duchek. Obtained funding: Xiong, Balota, Storandt, Head, and Morris. Administrative, technical, and material support: Buckles, Fagan, Holtzman, Duchek, Mintun, Grant, Snyder, Csernansky, and Morris. Study supervision: Storandt, Mintun, Benzinger, and Morris.
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REFERENCES


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