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Maternal dementia age at onset in relation to amyloid burden in non-demented elderly offspring

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ABSTRACT

Family history (FH) of dementia is a major risk factor for Alzheimer's disease, particularly when the FH is maternal and when the age of dementia onset (AO) is younger. This study tested whether brain amyloid-beta deposition, measured in vivo with ^{11}C-Pittsburgh compound B (PiB), was associated with parental dementia and/or younger parental AO. Detailed FH and positron emission tomography (PiB) data were acquired in 147 nondemented aging individuals (mean age 75 ± 8). No participant had both positive maternal and paternal FH. A series of analyses revealed that those with maternal, but not paternal, FH had greater levels of PiB retention in a global cortical region than those without FH. PiB retention in maternal FH was not significantly greater than paternal FH. Younger maternal dementia AO was related to greater PiB retention in offspring, whereas younger paternal dementia AO was not. Overall, results suggest that not only is amyloid-beta burden greater in individuals with maternal FH, but also that the burden is greater in association with younger maternal AO.

1. Introduction

Although the genetic basis of early-onset Alzheimer's disease (AD) is known to include the autosomal dominant inheritance of specific mutations, the genetics of more typical, late-onset AD has been much more difficult to elucidate (Mayeux, 2003). In addition to age as a prominent risk factor for AD (Mayeux, 2003), another major factor that confers additional risk is family history (FH), particularly when it involves the parents (Jarvik and Blazer, 2005; Jarvik et al., 2008; Silverman et al., 2003, 2005), and much of the FH risk has been attributed to the e4 allele of the apolipoprotein E (APOE) genotype (Mayeux, 2010). An interaction of APOE e4 effects and gender is widely recognized (Miech et al., 2002), and evidence for a maternal transmission factor for AD has been reported (Duara et al., 1993; Edland et al., 1996); however, controlling for age and female longevity, the data have been inconsistent (Ehrenkrantz et al., 1999; Heggeli et al., 2012). To explore the biological basis of these risk factors, investigators have evaluated AD-imaging endophenotypes, with specific focus on maternal FH. Thus, AD-like changes in regional brain volume (Berti et al., 2011; Honea et al., 2010), ^{18}F-fluorodeoxyglucose (FDG) metabolism (Mosconi et al., 2007), and amyloid-beta (Aβ) deposition (Honea et al., 2012; Mosconi et al., 2010) have been reported in nondemented subjects with maternal FH in excess of what is seen in groups of subjects with no FH or in those with a paternal FH. Importantly, these changes have been detected even when controlling for APOE e4 carrier status.

To further explore this phenomenon, we collected FH and positron emission tomography (PET) data for 147 nonimpaired older adults. We hypothesized that younger parental age of dementia onset (AO) would relate to greater Aβ burden and that the effect would be greater in those with a maternal history of dementia. A complicating factor in the analysis was that age of onset

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of dementia was not available for mothers who did not experience onset of dementia; i.e., it is right-censored by the age at which the mother was last known to be alive without dementia. We handled this feature through special treatment in linear regression of Aβ in offspring on maternal AO and through reverse proportional hazards regression models of maternal AO on offspring Aβ.

2. Methods

2.1. Sample

Participants (n = 147) were enrolled in longitudinal studies of aging and dementia at Massachusetts General and Brigham and Women's Hospitals, which were approved by the Partners Human Research Committee. All participants were evaluated with subject and informant interviews as well as cognitive testing and had a Clinical Dementia Rating (CDR; Morris, 1993) global score of 0 or 0.5, which included cognitively normal participants, participants who would be best characterized as having subjective cognitive concerns, and nondemented participants who met mild cognitive impairment (MCI) criteria. None of the participants had any neurologic or medical illness or any history of alcoholism, drug abuse, or head trauma. All scored 11 or lower on the 30-item Geriatric Depression Scale (Yesavage et al., 1983), 22 or higher on the Mini Mental State Examination (Folstein et al., 1975), and 93 or higher on the American National Adult Reading Test (Ryan and Paolo, 1992).

A parental history questionnaire, described below, yielded information about 279 biological parents of the 147 participants. Fifteen of the 147 participants were able to provide FH information about only 1 parent, as information about the other parent was unknown; these 15 were excluded from analyses in which we required definitive parental FH from both parents but were included in others.

2.2. Parental history questionnaire

Participants were classified into offspring groups according to parental history of dementia, using a questionnaire administered in person or by telephone. Each was asked whether either parent had a progressive dementia syndrome, and whether it was physician-diagnosed. No formal distinction was made between subjective reports of dementia and actual diagnosis of dementia or AD in a parent, since we did not have access to parents' medical records, and furthermore, AD was rarely diagnosed when these parents were elderly. Participants who could not recall a diagnosis of dementia in their parents were read a short list of typical dementia symptoms, to assist in determining whether dementia was present. They were also queried as to parents' major medical illnesses, causes of death, ages at death, and ages at dementia symptom onset.

2.3. PiB–PET imaging in offspring

Carbon-11 Pittsburgh compound B (PiB) was synthesized, and PET data were acquired and processed as described previously (Becker et al., 2011; Rentz et al., 2010). Briefly, after a transmission scan, 8.5–15 mCi 11C-PiB was injected as a bolus, followed immediately by a 60-minute dynamic acquisition. Each frame was evaluated to verify adequate count statistics and absence of head motion. PiB retention was expressed as the distribution volume ratio using cerebellar cortex as a reference tissue (Logan et al., 1990). Regions of interest were defined using the Automated Anatomic Labeling method (Tzourio-Mazoyer et al., 2002). An aggregate of cortical regions that have historically displayed elevated PiB burden in AD dementia (termed FLR: frontal, lateral parietal, lateral temporal, and retrosplenial cortices) was used for analysis, as described previously (Gomperts et al., 2008).

2.4. Statistical analysis: models relating FH to PiB retention

Fisher's exact test was used for tests of FH association of categorical variables and Wilcoxon rank sum tests or Kruskal–Wallis tests were used for continuous variables. Exact Wilcoxon tests were used when sample sizes were small enough to permit the computational burden. Models included terms for age of the offspring participants (coded as categorical according to the tertiles of its distribution: <70, 70–81, >81), CDR (0 vs. 0.5), gender of offspring, and years of education.

The reader is referred to Table 1 to serve as a guide to analyses and associated comparison groups below. Linear regression models were fit for PiB retention and treated FH as a binary variable in

Table 1
Analysis characteristics

Analysis #	1	2	3	4
Model type	Linear regression	Linear regression	Linear regression	Hazard regression
Purpose	PiB comparison of those with: maternal FH versus those without FH; paternal FH versus those without FH.	PiB comparison of those with: maternal FH versus no maternal FH; paternal FH versus no paternal FH.	Association of parent AO (continuous) with offspring PiB retention.	Alternative analysis for association of parent AO and offspring PiB retention.
N	65 PET subjects, (offspring; subset with dementia status known for both parents).	147 PET subjects (offspring; dementia status known for at least one parent).	25 PET subjects (offspring).	147 PET subjects (offspring).
Comparison groups and details	7 FHmat+ (subset), 7 FHpat+ (subset), and 51 FHneg.	13 FHmat+ versus 93 FHmat− 12 FHpat+ versus 79 FHpat−.	13 FHmat+ and 12 FHpat+.	AO or age at death without dementia data for one or both parents of 147 PET subjects.
Corresponding demographics table #	3	2	2	2

FHmat+ = positive maternal dementia history at parent age 75, regardless of whether paternal status was known.
FHmat− = negative maternal dementia history at parent age 75, regardless of whether paternal status was known.
FHmat+ (subset) = subset of FHmat+: positive maternal history of dementia, negative paternal history of dementia at parent age 75.
FHpat+ = positive paternal dementia history at parent age 75, regardless of whether maternal status was known.
FHpat− = negative paternal dementia history at parent age 75, regardless of whether maternal status was known.
FHpat+ (subset) = subset of FHpat+: positive paternal history of dementia, negative maternal history of dementia at parent age 75.
FHneg = negative history of dementia in both parents at parent age 75.
Key: AO, parental dementia age of onset; FH, family history of dementia; PET, positron emission tomography; PiB, pittsburgh compound B.