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Neurobiology of Aging 34 (2013) 22–34

NEUROBIOLOGY OF AGING

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Amyloid and metabolic positron emission tomography imaging of cognitively normal adults with Alzheimer's parents

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Received 31 May 2011; received in revised form 13 February 2012; accepted 1 March 2012

Abstract

This study examines the relationship between fibrillar beta-amyloid (Aβ) deposition and reduced glucose metabolism, a proxy for neuronal dysfunction, in cognitively normal (NL) individuals with a parent affected by late-onset Alzheimer's disease (AD). Forty-seven 40–80-year-old NL received positron emission tomography (PET) with ^{11}C-Pittsburgh compound B (PiB) and 18F-fluoro-2-deoxy-D-glucose (FDG). These included 19 NL with a maternal history (MH), 12 NL with a paternal history (PH), and 16 NL with negative family history of AD (NH). Automated regions of interest, statistical parametric mapping, voxel-wise intermodality correlations, and logistic regressions were used to examine cerebral-to-cerebellar PiB and FDG standardized uptake value ratios across groups. The MH group showed higher PiB retention and lower metabolism in AD regions compared with NH and PH, which were negatively correlated in posterior cingulate, frontal, and parieto-temporal regions (Pearson $r \leq -0.57$, $p \leq 0.05$). No correlations were observed in NH and PH. The combination of Aβ deposition and metabolism yielded accuracy $\geq 69\%$ for MH vs. NH and $\geq 71\%$ for MH vs. PH, with relative risk = 1.9–5.1 (*p values* < 0.005). NL individuals with AD-affected mothers show co-occurring Aβ increases and hypometabolism in AD-vulnerable regions, suggesting an increased risk for AD.
Published by Elsevier Inc.

Keywords: Alzheimer's disease; Family history; PET imaging; Amyloid; Glucose metabolism; Early detection

1. Introduction

Having a parent affected by late-onset Alzheimer's disease (LOAD) is a major risk factor among cognitively normal (NL) individuals (Bertram et al., 2010; Farrer et al., 1989). The genetics of LOAD remain, however, elusive, and biological mechanisms conferring risk are largely unknown.

Studies of known genetic mutations in early-onset familial AD indicate a primary role for beta-amyloid (Aβ) pathology in AD (Haass and Selkoe, 2007). Recent studies with positron emission tomography (PET) demonstrated increased ^{11}C-Pittsburgh compound B (PiB) retention, reflecting fibrillar Aβ deposits, in AD and mild cognitive impairment (MCI) patients compared with control subjects (Edison et al., 2007; Engler et al., 2006; Forsberg et al., 2008; Furst et al., 2012; Grimmer et al., 2010; Jack et al., 2009; Jagust et al., 2009; Kemppainen et al., 2006, 2007;

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0197-4580/$ – see front matter Published by Elsevier Inc.
10.1016/j.neurobiolaging.2012.03.002

Klunk et al., 2004, 2006; Li et al., 2008; Price et al., 2005). As a large proportion of nondemented elderly persons also exhibit substantial amyloid burden (Aizenstein et al., 2008; Mintun et al., 2006; Mormino et al., 2009; Pike et al., 2007; Storandt et al., 2009), the functional significance of elevated Aβ in this population is unclear. Histology studies have shown that among individuals with Aβ pathology, those with accompanying neuronal dysfunction are more likely to develop dementia in life than those without (Bennett et al., 2006; Price and Morris, 1999). Neuronal loss strongly correlates with AD symptoms (Terry et al., 1991), whereas Aβ load does not (Bennett et al., 2006; Price and Morris, 1999). Thus, individuals harboring Aβ burden and neuronal dysfunction are at conceivably higher risk for AD dementia than those showing Aβ pathology alone (for review, see Jack et al., 2010; Mosconi et al., 2010a).

Among NL persons with LOAD parents, those with a maternal history (MH) show increased Aβ deposition on PiB-PET compared with those with a paternal history (PH) and control subjects with negative history of AD (NH) (Mosconi et al., 2010d). Additionally, NL MH individuals show progressive hypometabolism on PET using 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) as the tracer compared with PH and NH (Mosconi et al., 2007, 2009). FDG-PET has long been used to detect presumably indirect functional effects of neurodegeneration in AD, using FDG as the tracer to measure resting-state cerebral metabolic rates of glucose as a proxy for neuronal activity (Sokoloff et al., 1977) and as a marker of synaptic density (Rocher et al., 2004). Synaptic dysfunction and loss induce a reduction in neuronal energy demand that results in decreased glucose metabolism and can be visualized at the tissue level using FDG-PET (for review see Herholz, 2003; Mosconi, 2005).

However, previous studies were performed in different subjects, and there are currently no published studies that simultaneously examined Aβ load, hypometabolism, and their combined effects in NL at risk for LOAD. This article shows that among NL with LOAD-affected parents, those with MH have increased Aβ deposition and glucose hypometabolism compared with those with PH and NH, and that these two markers provide converging and complemental information on AD risk in yet-asymptomatic individuals.

2. Methods

2.1. Subjects

This study examined a cohort of 65 consecutive NL individuals enrolled in ongoing longitudinal PET studies at New York University (NYU) and Turku University (Finland). Subjects were derived from multiple community sources, including individuals interested in research participation, family members, and caregivers of impaired patients. All subjects provided written informed consent to participate in this Institutional Review Board (IRB)-approved study.

Individuals with medical conditions or history of significant conditions that may affect brain structure or function, that is, stroke, diabetes, head trauma, any neurodegenerative diseases, depression, MRI evidence of hydrocephalus, intracranial mass, and infarcts including lacunes, and those taking psychoactive medications were excluded. Subjects were 40–80 years of age, had Clinical Dementia Rating (CDR) = 0, Global Deterioration Scale (GDS) ≤ 2, Modified Hachinski Ischemia Scale < 4, and normal cognitive test performance for age and education, as described elsewhere (Kemppainen et al., 2006; Mosconi et al., 2010d). ApoE genotype was determined using standard polymerase chain reaction procedures.

A family history of AD that included at least one first-degree relative whose AD onset was after age 60 years was elicited by using standardized family history questionnaires (Mosconi et al., 2009, 2010d). Participants were asked to fill in names, dates of birth, age at death, cause of death, and clinical information of all affected family members. The information was confirmed with other family members by interview with the examining neurologist, discussing the parents' symptomatology and progression of disease. All subjects were asked to provide as detailed as possible information about their parents' diagnosis, available medical records, and the parents' medication list. Some volunteers were children or caregivers of AD patients at both centers, for whom full medical records and/or autopsy reports were readily available for inspection. For the remaining subjects, when possible, we followed-up with the clinician who made the diagnosis to confirm the reports. Among the larger pool of possible recruits, only NL subjects whose parents' diagnosis of AD was reportedly clinician certified were included in this study. Subjects were not included if their parents had not lived to at least age 65 years. Only NL subjects whose parents' diagnosis of LOAD was reportedly clinician certified, and whose parents had lived to age ≥ 65 years were included in this study and divided into three groups: MH (i.e., only the mother had AD), PH (i.e., only the father had AD), and NH (i.e., neither parent had AD).

PiB-PET scans of 35 of 47 subjects were included in a previous publication (Mosconi et al., 2010d). The remaining 12 PiB scans and all 47 FDG scans were not previously examined for family history effects.

2.2. PET acquisition and preprocessing

Subjects received two PET scans acquired in three-dimensional mode on a GE PET scanner (NYU: LS Discovery, Turku: Advance; GE Medical Systems, Milwaukee, WI, USA) (Kemppainen et al., 2006, 2007; Li et al., 2008; Mosconi et al., 2010d). Briefly, before PET imaging, an antecubital venous line was positioned for isotope injection. Subjects rested with eyes open and ears unplugged in the quiet and dimly lit scan room. After injection of 15 mCi (~550 MBq) of *N*-methyl[^{11}C]2-(4'-methylaminophenyl)-6-hydroxy-benzothiazole (PiB), subjects were positioned in the scanner using laser light beams for head alignment. Total PiB scanning time was 90 minutes. The FDG scan was done 30 minutes after completion of the PiB scan or on a separate day. After an overnight fast, subjects were injected with 5 mCi (~340