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Periodontal disease associates with higher brain amyloid load in normal elderly

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ABSTRACT

The accumulation of amyloid-β (Aβ) plaques is a central feature of Alzheimer's disease (AD). First reported in animal models, it remains uncertain if peripheral inflammatory and/or infectious conditions in humans can promote Aβ brain accumulation. Periodontal disease, a common chronic infection, has been previously reported to be associated with AD. Thirty-eight cognitively normal, healthy, and community-residing elderly (mean age, 61 and 68% female) were examined in an Alzheimer's Disease Research Center and a University-Based Dental School. Linear regression models (adjusted for age, apolipoprotein E, and smoking) were used to test the hypothesis that periodontal disease assessed by clinical attachment loss was associated with brain Aβ load using ^{11}C-Pittsburgh compound B (PIB) positron emission tomography imaging. After adjusting for confounders, clinical attachment loss (≥3 mm), representing a history of periodontal inflammatory/infectious burden, was associated with increased PIB uptake in Aβ vulnerable brain regions ($p = 0.002$). We show for the first time in humans an association between periodontal disease and brain Aβ load. These data are consistent with the previous animal studies showing that peripheral inflammation/infections are sufficient to produce brain Aβ accumulations.

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1. Introduction

Worldwide, >35 million persons suffer from dementia among which 50%–60% are diagnosed with Alzheimer's disease (AD) (Alzheimer's Association, 2014). It is estimated these numbers will double by 2030 and double again by 2050. These statistics underline the enormous public health importance of identifying modifiable risk factors.

The accumulation of amyloid-β (Aβ) plaques is a central feature of AD whose cause is poorly understood. Postmortem studies have shown that amyloid accumulation can start as early as 30 years of age and increases with age (Braak and Braak, 1997; Kok et al., 2009). These findings have been confirmed by the imaging studies (Jack et al., 2009; Klunk et al., 2004; Landau et al., 2012). The results of clinical trials designed to remove brain amyloid from impaired individuals have been largely unsuccessful possibly because of the late intervention (Holmes et al., 2008; Morgan, 2011; Ozudogru and Lippa, 2012). This has placed a great emphasis on identifying factors and mechanisms that promote brain amyloid deposition in advance of symptoms.

Both animal models and clinical evidence show that inflammation is involved in the pathogenesis of AD (Akiyama et al., 2000; Griffin et al., 1998; Holmes and Butchart, 2011; McGeer et al., 2006; Tanzi, 2012), but it remains unknown which peripheral inflammatory and infectious conditions play a role and at which stage of AD development (Kamer et al., 2008a, 2008b; Miklossy, 2011a, 2011b). We examined human periodontal disease as a model for testing the relationship between peripheral inflammation/infections and brain Aβ. Periodontal disease is a chronic, peripheral, polymicrobial

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infection (Socransky and Haffajee, 1997) characterized by local and systemic inflammations. Periodontal disease is defined by the loss of the tissues surrounding the teeth, clinically defined by clinical attachment loss (CAL) (Demmer et al., 2008).

The present cross-sectional study used positron emission tomography (PET) amyloid imaging and clinical periodontal examinations to test the hypothesis that in cognitively normal subjects, the magnitude of periodontal disease burden is associated with the brain amyloid load.

2. Methods

2.1. Study subjects and design

Thirty-eight cognitively normal healthy subjects were included in this study. All subjects were participants in the National Institutes of Health (NIH)–supported AD studies at the New York University (NYU) School of Medicine. Subjects were recruited from a random community sampling of voter registration lists. Among the 250 elderly individuals who were contacted and invited to participate, 70 subjects agreed to participate. Of these, 40 subjects had standardized medical and cognitive examinations consistent with the National Alzheimer Coordinating Center guidelines (Beekly et al., 2007). The standardized diagnostic evaluation at the NYU School of Medicine consisted of medical, psychiatric, neuropsychological, apolipoprotein E (ApoE) genotyping, magnetic resonance imaging (MRI) examinations, and standardized periodontal examinations. Thirty-eight subjects also participated in ^{11}C-Pittsburgh compound B (PIB)-PET amyloid brain imaging performed at the Cornell Medical Center. All subjects provided written informed consent to participate in this institutional review board –approved study. The average interval between the PET scan and the periodontal examination was 1.29 $\pm$ 0.89 years. All research measures were performed blinded to the clinical data.

2.1.1. Inclusion criteria

All included subjects had at least 12 years of education and were fluent English speakers. Subjects were defined as cognitively normal if they had Clinical Dementia Rating =0 (Berg, 1984), Global Deterioration Scale $\leq$2 (Reisberg et al., 1982), and Mini-Mental State Examination $\geq$28 (Cockrell and Folstein, 1988).

All subjects were required to have a minimum of 10 evaluable teeth (Stein et al., 2007) and to have the physical capacity to manage their personal dental hygiene.

2.1.2. Exclusion criteria

Individuals were excluded if they had history/medical conditions that could affect brain structure or function, such as clinical or MRI evidence of cortical stroke, uncontrolled hypertension, diabetes, head trauma with loss of consciousness, any manifest neurodegenerative disease, chronic depression, MRI evidence of hydrocephalus, or intracranial mass. Subjects taking anti-inflammatory medications for chronic conditions (i.e., nonsteroidal anti-inflammatory drugs, anti-tumor-necrosis factor α) or antibiotics or having periodontal treatment 3 months before the periodontal evaluation were also excluded.

2.2. Clinical evaluations

2.2.1. Measures of periodontal disease

The assessment for periodontal disease was conducted as follows: teeth were counted, and the presence of dental plaque on 6 surfaces of all teeth was recorded (Silness and Loe, 1964). CAL, the primary dependent variable, was measured using a Michigan probe (Demmer et al., 2008) and recorded in millimeters at 6 sites per tooth. CAL defined the long-term periodontal inflammatory/infectious condition. CAL was obtained by adding the probing depth (PD) to the distance from the free gingival margin to the cementoenamel junction (positive if the gingival margin is apical to the cement-enamel junction and negative if it is coronal). The PD was measured as the linear distance in millimeters from the gingival margin to the base of the periodontal pocket. Bleeding on probing (BOP) was assessed at each probing site.

The primary periodontal exposure was defined as the cumulative number of sites with CAL $\geq$3 mm (CAL3) and provided a measure of periodontal disease burden (Tonetti et al., 2005). The use of CAL3 was based on our a priori hypothesis proposing a linear relationship between the magnitude of periodontal destruction because of the history of periodontal inflammation and brain amyloid accumulation, a chronic process. The threshold of 3 mm also included milder forms of the periodontal disease. These measures were used previously to define relationships between periodontal and cardiovascular diseases and cognitive dysfunction (Beck et al., 2001; Elter et al., 2004). An additional consideration came from the evidence showing that CAL associated better with a chronic systemic process (Demmer et al., 2008) rather than an acute one. CAL are accepted measures of cumulative lifetime experience of periodontitis, and using these measures, the fifth European Workshop in Periodontology proposed the following case definition for periodontitis: the presence of proximal attachment loss of $\geq$3 mm in at least 2 nonadjacent teeth. All our subjects had CAL3 on multiple teeth; thus, they all fell within this case definition. To show consistency in the relationship between measures of periodontal disease and brain amyloid accumulation, other measures of periodontal disease were evaluated: CAL $\geq$4 mm (CAL4) (Page and Eke, 2007), PD $\geq$3 mm (PD3), and BOP. By comparison with CAL, PD and BOP measure the present disease and inflammation. To further define periodontal disease, we combined historical with current measures of periodontal disease: the presence of CAL3 at $\geq$66% sites and concomitant PD $\geq$5 mm (PD5) was defined as Perio1 (Jonsson et al., 2014).

2.2.2. PET outcome variables

2.2.2.1. Acquisition and preprocessing. Subjects received a PIB-PET scan acquired in 3-dimensional mode on an LS Discovery PET scanner (GE Medical Systems, Milwaukee, WI, USA) (Li et al., 2008; Mosconi et al., 2010, 2013a). Briefly, as previously reported, subjects were injected with 15 mCi (550 MBq) of *N*-methyl[11C]2-(4'-methylaminophenyl)-6-hydroxy-benzothiazole, PIB, followed by a 90-minute PET data acquisition (Mosconi et al., 2010). Image analysis was carried out at NYU, blind to the clinical data. For each subject, summed PET images corresponding to the 60- to 90-minute PIB data were coregistered to the subject's T1 MRI scan using Statistical Parametric Mapping (SPM). Both the summed 60- to 90-minute PIB image and SPM2-segmented MRI gray-matter (GM) and white-matter images were reformatted into SPM's standard template space. In the standard space, regions of interest (ROIs) were intersected with the GM to exclude all non-GM pixels. HIPMASK was used for accurate ROI sampling (Li et al., 2008; Mosconi et al., 2005). A correction for partial volume effects was done using the 2-tissue method of Muller-Gartner, which corrects for both cerebrospinal fluid and white-matter tracer uptake (Muller-Gartner et al., 1992).

2.2.2.2. PET ROIs. The average PIB intensity in each ROI was normalized by the average intensity from a cerebellar GM reference ROI, to create the standard uptake value ratio (SUVR). From our previous work (Li et al., 2008; Mosconi et al., 2013b), 5 bilateral ROIs known to be vulnerable to amyloid depositions were sampled to create a composite neocortical PIB_{AD} mask (MaskAD), which was the primary outcome measure. The regions included in the AD mask were prefrontal cortex, middle frontal gyrus, lateral temporal

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