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Cognitive deficits in non-demented diabetic elderly appear independent of brain amyloidosis

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ABSTRACT

Background: To determine the effects of Type 2 diabetes (DM2) on levels of brain amyloidosis and cognition in a community-dwelling cohort of nondemented elderly individuals.
Methods: 33 subjects (16 DM2, 17 nondiabetic) were prospectively recruited. Subjects underwent a PET scan using the amyloid tracer, Pittsburgh Compound B, and a neuropsychological evaluation. Associations between DM2, brain amyloidosis, and cognition were assessed using multivariate regressions, adjusting for age and APOE4 status.
Results: DM2 subjects had lower global cognitive function ($p = 0.018$), as measured by the Repeatable Battery for the Assessment of Neuropsychological Status. There was no difference in brain amyloidosis between groups ($p = 0.25$).
Conclusions: Community-dwelling, nondemented individuals with DM2 had greater cognitive deficits, which do not appear to be mediated by brain amyloidosis. Further studies exploring potential mediators of these cognitive deficits should be performed.

1. Introduction

Both Type 2 diabetes (DM2) and Alzheimer's disease (AD) are major public health problems and sources of morbidity among older adults. With the burgeoning obesity epidemic, it is estimated that 285 million people worldwide carry a diagnosis of DM2 [1]. Thirty-four million people are estimated to suffer from dementia, with 70% of these cases attributable to AD [2]. Many epidemiologic studies have found that DM2 increases the risk of developing dementia [3–7]. However, the degree to which this increased risk is related to underlying AD pathology, such as brain amyloidosis, is unknown.

The pathological hallmark of AD is brain amyloidosis on autopsy [8]. Some have hypothesized that hyperglycemia in DM2 patients could prompt formation of advanced glycation endproducts [9], leading to increased beta-amyloid plaque aggregation in the brain [10–12]. Others have hypothesized that high plasma insulin levels among DM2 subjects, secondary to insulin resistance at the tissue level, result in greater diversion of the insulin-degrading enzyme from its usual function of degrading amyloid [13], thereby increasing brain amyloidosis. However, two prior retrospective studies have not found increased brain amyloidosis in DM2 [13,14]. Possible reasons these studies did not find increase brain amyloidosis could be that they included cohorts with relatively mild DM2 disease [13], elderly subjects who already had age-related amyloid deposition [14], and mixed cohorts including subjects with mild cognitive impairment (MCI) and AD [14], making it difficult to separate out the effects of DM2.

Since it is estimated that brain amyloidosis begins approximately 15–20 years before onset of cognitive symptoms [15], we aimed to enroll a younger cohort of DM2 individuals than previously reported. Furthermore, it has been reported that diabetic patients with longer disease duration, greater severity of disease, and diabetic complications have a higher rate of cognitive impairment [16], so these high-risk individuals were enrolled into our study. Finally, we enrolled subjects who did not

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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meet criteria for mild cognitive impairment (MCI) or AD to exclude potential confounding by pre-existing AD pathology, irrespective of the effects of DM2.

The purpose of this study, therefore, was to determine the effects of DM2 on brain amyloid deposition in vivo in a prospectively-enrolled, nondemented cohort, using positron emission tomography (PET) with the amyloid tracer, Pittsburgh Compound B (PiB). Furthermore, we evaluated the association between DM2 and cognitive deficits, investigating potential mediators of disease.

2. Materials and methods

2.1. Subjects

We prospectively enrolled 33 subjects in this study: 16 with diagnosed DM2 and 17 non-diabetic age-matched cognitively normal individuals. Individuals were recruited through flyers posted in the community, newspaper advertisements, and ambulatory care clinics. All subjects gave written informed consent for participation in this study, and this study was approved by the Institutional Review Board.

In order to target subjects with long-standing or severe diabetes, who may have the greatest risk of developing AD [16], inclusion criteria for DM2 subjects included at least one of the following: [1] DM2 diagnosed 10 or more years ago, [2] recent HbA1c level of 7% or greater, [3] history of a DM2-related complication, such as retinopathy, nephropathy, or neuropathy, or [4] recently reported blood glucose levels of >300 mg/dl.

All subjects were between the ages of 55 and 75, lived independently in the community, and were able to perform all routine activities of daily living. Subjects were excluded if they had significant comorbid medical conditions that could impact brain function, including major psychiatric disorders (i.e. major depression, bipolar disorder, and psychosis), brain tumors, prior strokes, significant traumatic brain injury (defined as requiring a visit to the emergency department or a hospital stay), seizure disorders, recent illicit drug use, alcohol abuse, and major medical problems, such as heart failure, recent myocardial infarction, renal failure, liver disease, chronic obstructive pulmonary disease, and malignancy. Medical records were also reviewed for exclusionary criteria.

2.2. Clinical data

To determine what aspect of DM2 may be related to brain amyloidosis or cognition, all subjects completed detailed questionnaires about their medical history, and medical records were also examined. Clinical data included duration of disease, recent hemoglobin A1c values, recent blood glucose readings, medications used to control DM2, and presence of diabetic complications, such as retinopathy, neuropathy, or nephropathy.

Clinical data for all subjects included recent weight and height, cholesterol levels, blood pressure measurements, smoking history, and exercise regimens, since these variables have been reported as affecting for AD [17,18]. We also elicited a family history of dementia, since genetics could explain increased brain amyloidosis in otherwise cognitively normal individuals [19].

Subjective memory complaints were elicited by the questions, “are you forgetful?” and “do you have difficulty remembering things?” Subjective memory complaints were further assessed by the Cognitive Change Index [20], Patients with subjective memory complaints, despite normal cognition on objective measures, have been shown to have greater longitudinal cognitive decline [21,22]. Finally, since health literacy has been shown to affect health outcomes, including complications of DM2, all subjects also completed a health literacy questionnaire called the Short Test of Functional Health Literacy in Adults (STOFHLA) [23,24].

2.3. Cognitive battery

Cognitive testing was performed by the Director of Neuropsychology at our institution with 20 years of experience in evaluating patients with memory disorders. Cognitive assessment was performed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which includes measures for immediate and delayed memory, visuospatial and constructional function, attention, and language [25]. Briefly, immediate and delayed memory were tested using tasks that involved recalling a list of words and a short story. Visuospatial and constructional function was tested using figure copying and line orientation tasks. Attention was tested using digit span and coding tasks. Language was tested using picture naming and semantic fluency tasks. The RBANS has been found to have almost 90% accuracy for discriminating between cognitive normal individuals and those with mild cognitive impairment [25]. Cognitive processing speed and executive function were also evaluated using the Trail Making Test [26,27], with Part A measuring visual scanning and motor speed and Part B measuring executive function related to mental sequencing. Patients were also screened for comorbid depression and anxiety using the Beck Depression Inventory-II [28] and the Beck Anxiety Inventory [29] and excluded as necessary.

2.4. APOE genotyping

Blood was drawn from all subjects to isolate DNA for APOE genotyping, which was performed using polymerase chain reaction amplification, allele-specific primers, and identification of fragments on an agarose gel [30].

2.5. PiB PET image acquisition, template creation, and analysis

All subjects underwent an amyloid PET scan on a Siemens Biograph PET—CT scanner [Siemens, Knoxville, TN; 1 mm FWHM, 25 cm FOV] using a standardized research protocol [19]. Briefly, all patients received an intravenous catheter for injection of 15 mCi of PiB. Sixty minutes after injection, subjects were scanned for 30 min with their eyes open in a quiet, dimly lit room. A low-dose CT scan was acquired for attenuation correction, and all images were reconstructed into a 512×512 matrix.

Summed PET images corresponding to the 60–90 min of PiB data were generated and nonlinearly normalized to a PiB template. The PiB template was generated by averaging the summed images of 48 cognitively normal individuals in the same age range, which were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) online data repository. Orientation and origin for all the PiB PET images were automatically fixed to the anterior commissure to match the templates used in Statistical Parametric Mapping (SPM, Wellcome Trust Center for Neuroimaging), since SPM's “normalize” function uses the origin as a starting estimate. These reoriented PiB PET images and the mean PiB template were skull-stripped with the Brain Extraction Tool from FMRIB Software Library (FSL) [31] to avoid any bias induced by skull staining. All the skull-stripped PiB PET images were then nonlinearly warped to the skull-stripped mean PiB template. Gray matter regions were parcellated using the Automated Anatomical Labeling (AAL) atlas to obtain 116 automated regions-of-interest [32] See Fig. 1. Regional PiB uptake values were then normalized by the subject's cerebellar reference uptake.

The ADNI is a longitudinal, multicenter, observational cohort study, which was designed to identify imaging and biochemical biomarkers for diagnosis and monitoring of AD [33]. The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging