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High normal fasting blood glucose is associated with dementia in Chinese elderly

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Abstract

Background: Diabetes is a risk factor for mild cognitive impairment (MCI) and dementia. However, the association between high normal fasting blood glucose (FBG) and dementia has not been studied.
Methods: Polytomous logistic regression was used to assess the association of dementia and MCI with FBG in an age- and sex-matched sample of 32 dementia patients, 27 amnestic MCI (aMCI) patients, and 31 normal controls (NC). Analyses were repeated for those with normal FBG. Correlations between FBG and cognitive test scores were obtained.
Results: Controlling for age, gender, education, body mass index, Hachinski Ischemic Score, magnetic resonance imaging (MRI) stroke, and normalized brain, hippocampal, and white matter hyperintensity MRI volumes; higher FBG was associated with dementia versus aMCI status (OR = 3.13; 95% CI, 1.28–7.69). This association remained (OR = 7.75; 95% CI, 1.10–55.56) when analyses were restricted to subjects with normal FBG. When dementia patients were compared with NC adjusting for age, gender, and education, a significant association with FBG also was seen (OR = 1.83; 95% CI, 1.09–3.08), but it was lost when vascular covariates were added to the model. FBG was not associated with aMCI status versus NC. Higher FBG was correlated with poorer performance on the Trail-making Test Part B ($P = .003$). The percentage of dementia patients with high normal FBG (90%) was significantly higher than that of aMCI patients with high normal FBG (32.9%) ($\chi^2 = 13.9$, $P < .001$).
Conclusions: Higher FBG was associated with dementia (vs. aMCI) independent of vascular risk factors and MRI indicators of vascular disease, and remained a significant risk factor when analyses were restricted to subjects with normal FBG. The results of this cross-sectional study suggest that a high normal level of FBG may be a risk factor for dementia.

Keywords: Dementia; Alzheimer's disease; Mild cognitive impairment; Fasting blood glucose; Diabetes; Hippocampal volume; White matter hyperintensity; Magnetic resonance imaging; Cognitive performance; Vascular risk

1. Introduction

Diabetes is a risk factor for dementia and mild cognitive impairment (MCI) [1–5] as well as for cognitive decline among older adults [6–8]. The mechanisms responsible for the link between diabetes, cognitive decline, and dementia are not well understood. Possible explanations include the effects of diabetes on the metabolism of beta amyloid [9] and on vascular ischemic disease [10].

Although high levels of fasting blood glucose (FBG) increase the risk of dementia and MCI [11], the association between variation in normal levels of FBG and these cognitive

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outcomes has not been addressed. Data from cross-sectional studies suggest that variation of normal FBG may be related to scores on episodic and working memory tasks [12,13].

In this study, we report the findings of a cross-sectional study of older adults in Shanghai, China, comparing cases of dementia with amnestic MCI (aMCI) cases and normal controls (NC). On the basis of previous work, we hypothesized that FBG in the pre-diabetic and diabetic range would be associated with aMCI and dementia in comparison with NC. To determine whether the association was restricted to those with high FBG, we explored the entire range of FBG levels with respect to associations with diagnosis and cognitive performance.

2. Methods

2.1. Study population

Subjects were participants in the Shanghai Community Brain Health Initiative-Pilot, a cross-sectional study of older persons living in Shanghai, China. Cases of dementia and MCI were identified from consecutive cases newly diagnosed in the Memory Disorders Clinic at Huashan Hospital between May, 2007 and November, 2008. A total of 109 cases of dementia and MCI and their informants were invited to participate; of these 58 were recruited (53.2%). Of the 51 not recruited, 42 refused, 8 were unreachable, and 1 had a stroke. The two principal reasons for refusal were that they had been examined recently in the clinic and did not wish to be examined again, or that they did not want to make the trip to return because either they lived too far away or it was too hot to travel. Because Huashan Hospital is a major teaching hospital, its patients represent the population of Shanghai and travel to the hospital can take considerable effort. Controls were identified using a government-maintained ''name list,'' which includes the name, gender, age, address, and telephone number of every resident in Shanghai. For this study, we obtained the name list for the Jing'an district where Huashan Hospital is located and focused on a resident group living in five buildings in the Jingansi Temple Community. Potential controls were approached at the door to describe the study. Of 71 potential participants from the name list, 10 refused (14%). An additional three names on the name list were unreachable. The recruitment rate in the community was 81.6%. When the 58 residents in the community were clinically evaluated, two met study criteria for dementia (3.5%) and 12 met Petersen criteria for MCI (20.6%). These individuals were added to the respective case pools. Of 116 eligible cases and controls, we frequency matched 32 NC, 34 MCI, and 34 dementia cases by age and gender for analyses. Among the MCI cases, 4 (12%) were found to have nonamnestic MCI, and 30 (88%) the amnestic type (aMCI). Because there was an insufficient number to analyze separately, nonamnestic MCI cases were excluded from subsequent analyses. Three participants were missing complete data on magnetic resonance imaging (MRI) volumes (one aMCI and two demented patients) and three were missing data on FBG (one NC and two aMCI patients), resulting in a final sample of 31 NC, 27 aMCI cases, and 32 dementia cases.

The study was approved by the Huashan Hospital, Fudan University in Shanghai, China, and the University of South Florida Institutional Review Boards. We obtained written informed consent from all cases and controls and their proxies.

2.2. Dementia diagnosis

All subjects received a detailed physical and neurologic evaluation by study neurologists (Q.Z. and Q.G.), a neuropsychological battery, MRI, and blood donation. The neuropsychological battery included the Chinese Cognitive Abilities Screening Instrument [14], WAIS-R Digit Span [15], Bell Cancellation Test [16], WMS Logical Memory Test [17] (immediate and delayed recall), Rey-Osterrieth Complex Figure [18] (copying and recall), Stroop Test [19], Auditory Verbal Learning Test [20], Category Verbal Fluency Test, WAIS-R Similarities Test [15], Trail-Making Test [21], Clock-Drawing Test [22], Boston Naming Test [23], and Mattis Dementia Rating Scale [24]. Consensus diagnostic conferences were conducted by the Chinese team (D.D., Q.Z., Q.G., Z.H.), with a subset of difficult cases also attended by members of the U.S. team (R.P., D.G., D.P.S., A.R.B., J.A.M.). Dementia and its subtypes were diagnosed with DSM-IV criteria [25], NINCDS-ADRDA [26] criteria for Alzheimer's disease, and NINDS-AIREN criteria for vascular dementia [27]. Qualitative MRI assessment was used in the diagnosis and subtyping of dementia; quantitative MRI ratings were performed independently (C.D.) without knowledge of diagnostic status.

2.3. MRI volumetric measures

Brain images were obtained at Huashan Hospital with a GE 1.5 T MRI. Imaging parameters were as follows (1) axial spin echo, T2-weighted double echo image, TE1 20 ms, TE2 90 ms, TR 2420 ms, FOV 24 cm, slice thickness 3 mm; (2) coronal 3D spoiled gradient recalled echo (IR-prepped SPGR) acquisition, T1-weighted image, TR 9.1 ms, flip angle 15 degrees, FOV 24 cm, slice thickness 1.5 mm; (3) axial FLAIR image, TE1 120 ms, TR 9000 ms, T1 2200 ms, FOV 24 cm; slice thickness 3 mm. The images were sent to the Imaging of Dementia and Aging Laboratory where image quantification was performed by a rater blinded to age, gender, educational achievement, and diagnostic status.

Analysis of brain and white matter hyperintensity (WMH) volumes was based on a FLAIR sequence designed to enhance WMH segmentation [28]. Brain and WMH segmentation was performed in a two-step process according to previously-reported methods [29,30]. Intra- and inter-rater reliability for these methods are high and have been published [31]. Boundaries for the hippocampus were manually traced according to previously reported methods [32] that