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Alzheimer's & Dementia 10 (2014) 18–26

Alzheimer's & Dementia

Association of diabetes with amnestic and nonamnestic mild cognitive impairment

Rosebud O. Roberts[a,b,*], David S. Knopman[b], Yonas E. Geda[a,c], Ruth H. Cha[d], V. Shane Pankratz[d], Luke Baertlein[e], Bradley F. Boeve[b], Eric G. Tangalos[f], Robert J. Ivnik[g], Michelle M. Mielke[a], Ronald C. Petersen[a,b]

[a]*Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA*
[b]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*
[c]*Department of Psychiatry and Psychology and Department of Neurology, Mayo Clinic, Scottsdale, AZ, USA*
[d]*Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN USA*
[e]*Rollins School of Public Health, Department of Epidemiology, Emory University, Atlanta, GA, USA*
[f]*Division of Primary Care Internal Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA*
[g]*Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA*

Abstract

Background: Type 2 diabetes may increase the risk of amnestic mild cognitive impairment (aMCI) through Alzheimer's disease (AD)-related and vascular pathology and may also increase the risk of nonamnestic MCI (naMCI) through vascular disease mechanisms. We examined the association of type 2 diabetes with mild cognitive impairment (MCI) and MCI subtype (aMCI and naMCI) overall and by sex.
Methods: Participants were Olmsted County, Minnesota residents (70 years and older) enrolled in a prospective, population-based study. At baseline and every 15 months thereafter, participants were evaluated using the Clinical Dementia Rating scale, a neurological evaluation, and neuropsychological testing for a diagnosis of normal cognition, MCI, and dementia by a consensus panel. Type 2 diabetes was ascertained from the medical records of participants at baseline.
Results: Over a median 4.0 years of follow-up, 348 of 1450 subjects developed MCI. Type 2 diabetes was associated (hazard ratio [95% confidence interval]) with MCI (1.39 [1.08–1.79]), aMCI (1.58 [1.17–2.15]; multiple domain: 1.58 [1.01–2.47]; single domain: 1.49 [1.09–2.05]), and the hazard ratio for naMCI was elevated (1.37 [0.84–2.24]). Diabetes was strongly associated with multiple-domain aMCI in men (2.42 [1.31–4.48]) and an elevated risk of multiple domain naMCI in men (2.11 [0.70–6.33]), and with single domain naMCI in women (2.32 [1.04–5.20]).
Conclusions: Diabetes was associated with an increased risk of MCI in elderly persons. The association of diabetes with MCI may vary with subtype, number of domains, and sex. Prevention and control of diabetes may reduce the risk of MCI and Alzheimer's disease.

Keywords: Mild cognitive impairment; Risk factors; Type 2 diabetes; Incidence; Cohort studies; Population-based studies; Sex differences; Diabetic retinopathy; Diabetic neuropathy

1. Introduction

Several studies have reported associations of type 2 diabetes mellitus with an increased risk of cognitive impairment and dementia [1–9], including Alzheimer's disease (AD) [8,10,11] and vascular dementia [11,12]. These studies suggest that type 2 diabetes may also be associated with mild cognitive impairment (MCI) subtypes: with amnestic MCI (aMCI) through both AD and vascular pathology, and with nonamnestic MCI (naMCI) through vascular disease mechanisms [2]. Despite this, there are few population-based studies on associations of type 2 diabetes with incident MCI subtypes.

Relationships between risk factors and cognitive impairment may differ based on study of subjects with incident versus prevalent cognitive impairment. The study of incident

*Corresponding author. Tel.: 507-538-0487; Fax: 507-284-1516.
E-mail address: roberts.rosebud@mayo.edu

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http://dx.doi.org/10.1016/j.jalz.2013.01.001

cases of MCI establishes a temporal association, includes a broad spectrum of disease severity, and may represent a progressive disorder. In contrast, prevalent cases may include more slowly progressive cases and may be influenced by survival bias. Furthermore, the identification of MCI subtypes on the basis of cognitive profiles may offer additional insights regarding severity because MCI subtypes reflect the extent of regional cortical involvement and the underlying etiology of the MCI. Single-domain MCI syndromes are likely to represent more circumscribed pathology, whereas multidomain MCI may represent more extensive disease. Amnestic presentations of MCI are more likely to be due to AD pathophysiology, whereas naMCI probably includes non-AD type conditions, especially cerebrovascular disease. Because of the pressing unanswered questions about the role of diabetes in dementing illness in regard to cerebrovascular versus AD pathways, the study of associations of type 2 diabetes with incident MCI subtypes and number of domains affected offers a novel approach to the mechanisms of diabetes in cognitive impairment and the impact of disease extent.

Previous studies have reported a sexual dimorphism in the occurrence of dementia, for AD in particular, with higher estimates in women than in men [13–15]. More recently, we and others have reported a sexual dimorphism in incidence and prevalence of MCI, but with higher estimates in men than in women [16–20]. Some imaging studies have also reported sex differences in brain aging that may partly explain the apparent discordance in the sexual dimorphism in the occurrence of dementia versus MCI [21–24]. Together, these studies and another that reported sex differences in inflammatory markers in men and women [25] suggest that risk factors for MCI vary in men and women and underscore the need to identify modifiable risk factors that have a differential impact on risk of MCI in men versus women. Therefore, the objective of this study was to investigate the association of type 2 diabetes mellitus with MCI and MCI subtypes overall, and by sex, in a population-based, prospective cohort enrolled in the Mayo Clinic Study of Aging.

2. Methods

2.1. Study cohort

We established the Mayo Clinic Study of Aging to estimate the incidence and identify risk factors for MCI in Olmsted County, MN. Details of the study design and participant recruitment are described in detail elsewhere [16,17,26]. In brief, we used the medical records-linkage system of the Rochester Epidemiology Project to construct a sampling frame of Olmsted County residents who were aged 70 to 89 years on October 1, 2004 (n = 9953) [27]. From an age- and sex-stratified random sample of 5233 subjects, 2719 (61.8%) of 4398 eligible subjects agreed to participate in the baseline assessment either in person (n = 2050; 46.6%; full participants) or by telephone (n = 669; 15.2%; telephone-only participants) [17,26].

The institutional review boards of the Mayo Clinic and of Olmsted Medical Center approved the study. Written informed consent was obtained for all participants who were examined as part of the study.

2.2. Clinical measurements

2.2.1. In-person evaluations

Each subject was evaluated by a nurse or study coordinator as well as a physician and underwent extensive cognitive testing by a psychometrist. The nurse interview included questions about memory administered to the participant, and the Clinical Dementia Rating scale and the Functional Activities Questionnaire were administered to an informant. The neurological evaluation included the Short Test of Mental Status [28], a medical history review, and a neurological examination. The cognitive testing used nine tests to assess function in four cognitive domains: memory, executive function, language, and visuospatial skills. The raw scores on each test were transformed into age-adjusted scores using normative data from Mayo's Older Americans Normative Studies and were scaled to have a mean of 10 and a standard deviation (SD) of 3 [29]. Domain scores were computed by summing the adjusted and scaled test scores within a domain and scaling again to allow comparisons across domains [17,26].

2.2.2. Diagnostic criteria for MCI

Performance in a specific cognitive domain was assessed by comparing the domain score with the score (means and SD) for normal subjects from the Olmsted County population [29]. Cognitive impairment was considered if the score was $\geq$1.0 SD below the mean; however, a final decision about impairment was based on a consensus agreement among the examining physician, nurse, and neuropsychologist, taking into account education, prior occupation, visual or hearing deficits, and other information [16,17,26].

A diagnosis of MCI was based on published criteria: cognitive concern by subject, informant, nurse, or physician; impairment in one or more of the four cognitive domains (from cognitive battery); essentially normal functional activities; and absence of dementia [17,26,30]. Subjects with MCI were classified as having aMCI if the memory domain was impaired; naMCI if the memory domain was not impaired, but one or more nonmemory domains were impaired; and as having single- versus multiple-domain MCI. A diagnosis of dementia was based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria. Subjects who performed within the normative range and did not meet criteria for MCI or dementia were considered to be cognitively normal [17,26,30].

2.2.3. Longitudinal follow-up

Participants were evaluated at 15-month intervals using the same protocol for clinical and cognitive findings as was used for full participants at baseline. Information from