Type 2 Diabetes and Late-Onset Alzheimer's Disease

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Key Words

Type 2 diabetes · Alzheimer's disease

Abstract

Background/Aims: To confirm in a cohort recruited in 1999–2001 our finding in a cohort recruited in 1992–1994 relating type 2 diabetes (T2D) to late-onset Alzheimer's disease (LOAD). **Methods:** Participants were 1,488 persons aged 65 years and older without dementia at baseline from New York City. T2D was ascertained by self-report. Dementia and LOAD were ascertained by standard research procedures. Proportional hazard regression was used for analyses relating T2D and LOAD. **Results:** The prevalence of T2D was 17%. There were 161 cases of dementia and 149 cases of LOAD. T2D was related to dementia (hazard ratio = 1.7; 95% confidence interval = 1.4–2.9) and LOAD (1.6; 1.0–2.6) after adjustment for age, sex, education, ethnic group and apolipoprotein E ε4. This association was weaker when only AD – excluding cases of mixed dementia – was considered (hazard ratio = 1.3; 95% confidence interval = 0.8–2.2). **Conclusion:** T2D is associated with LOAD. Cerebrovascular disease may be an important mediator.

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Introduction

The prevalence of type 2 diabetes (T2D) in the elderly population is already high and trends suggest a further increase. By estimates, 10% of the elderly already suffer from diabetes [1, 2]. Late-onset Alzheimer's disease (LOAD) is the predominant form of dementia, with an ever-increasing prevalence in the elderly; the number of AD patients is projected to quadruple by the year 2047 in the USA alone [3]. It has been estimated that as many as half of all individuals aged 85 years and older may have AD [4]. Like diabetes, dementia prevalence differs across ethnic groups and is more common among Blacks and Hispanics [5].

We previously found in a cohort recruited in 1992–1994 that a history of T2D was strongly associated with a higher risk of dementia, including LOAD [6]. The objective of this study was to explore the association between T2D and LOAD in a larger cohort recruited between 1999 and 2001.

Methods

Participants were recruited by random sampling of healthy Medicare eligible persons aged >65 years in several low-income neighborhoods with a high proportion of Hispanics in northern Manhattan. They were part of the Washington Heights-Inwood

Columbia Aging Project – a longitudinal population-based cohort in which clinical and epidemiological data are collected at regular intervals and vital status is continually updated. Recruitment occurred in two cohorts; recruitment for the first cohort began in 1992 and for the second cohort in 1999. This report is based on the cohort recruited in 1999. The geographic study area was the 14 census tracts comprising that area of Manhattan between approximately 155th and 181st Streets. Lists of all persons in receipt of Medicare or Medicaid in the study area were obtained from the Health Care Financing Administration. Potential study subjects were then drawn by systematic random sampling into 1 of 6 strata formed on the basis of ethnicity (Hispanics, non-Hispanic Blacks and non-Hispanic Whites) and age (65–74, ≥ 75 years). The cohort of 2,183 additional participants was formed in 1999 using generally similar methods. The main exceptions are as follows: new lists of beneficiaries were obtained but all those drawn into the 1992 cohort were excluded; within the course of contacting and arranging for the initial evaluation, participants who reported that a physician had diagnosed them with dementia were excluded; the study area was extended to the south and to the north and now encompassed all of Manhattan north of (approx.) 145th Street. For this refreshment cohort, recruitment letters were sent to a total of 7,120 persons living in households with a known phone number. Of these, 265 (3.7%) were found to have died, 1,541 (21.6%) no longer lived in the region, 662 (9.3%) were ineligible and 2,810 (39.5%) refused to participate. The total number recruited was therefore 2,174, and the overall recruitment rate for eligible individuals living in the study area for the refreshment cohort was 40%. Of the 2,174 persons in the 1999 cohort, 222 had dementia at baseline, and 462 had no follow-up. Thus, the final sample for these analyses was 1,488. Compared to the final sample (online suppl. table 1, www.karger.com/doi/10.1159/000324134), persons excluded due to baseline dementia were older, more likely to be Hispanic and less likely to be non-Hispanic White. Persons excluded due to loss to follow-up were older, less likely to be White and more likely to have T2D. Apolipoprotein E (APOE) $\epsilon 4$ data was available in 1,190 participants, and data of non-high-density lipoprotein (HDL) cholesterol and HDL cholesterol was available in 1,130 participants. Follow-up examinations were conducted approximately every 18 months and included neuropsychological assessments and medical history questionnaires.

Definition of Diabetes and Other Covariates

History of T2D was ascertained by self-report or by the use of diabetes medications at baseline and each follow-up visit. Hypertension, heart disease and smoking were defined by self-report. Heart disease included a history of atrial fibrillation and other arrhythmias, congestive heart failure, myocardial infarction and angina pectoris. Smoking was classified into never, current and past smoking. Fasting plasma total cholesterol and triglyceride levels were determined at the first follow-up using standard enzymatic techniques. HDL cholesterol levels were determined after precipitation of apolipoprotein-B-containing lipoproteins with phosphotungstic acid [7]. Low-density lipoprotein cholesterol was recalculated using the formula of Friedewald et al. [8]. APOE genotypes were determined as described by Hixson and Vernier [9] with a slight modification [10]. We classified persons as homozygous or heterozygous for the APOE $\epsilon 4$ allele or not having any $\epsilon 4$ allele.

Diagnosis of Dementia

The diagnosis of dementia was established based on all available information gathered from the initial and follow-up assessments. Dementia was determined by consensus at a conference of physicians, neurologists, neuropsychologists and psychiatrists. The diagnosis of dementia was based on standard research criteria [11] and required evidence of cognitive decline, including memory impairment, on the neuropsychological test battery as well as evidence of impairment in social or occupational function (clinical dementia rating >0.5) [12]. The diagnosis of LOAD was based on the criteria of the National Institute of Neurological and Cognitive Disorders and Stroke/Alzheimer's Disease and Related Disorders Association [13]. A diagnosis of *probable* LOAD was made when the dementia could not be explained by any other disorder. A diagnosis of *possible* LOAD was made when the most likely cause of dementia was AD, but there were other disorders that could contribute to the dementia such as stroke and Parkinson's disease. A diagnosis of vascular dementia (VD) was made in all subjects with dementia in whom stroke was judged to be the main cause of dementia based on evidence of the focal effects of the stroke, its temporal relationship with dementia (within 3 months of stroke), or both. Brain imaging was available in 85% of cases of stroke; in the remainder, World Health Organization criteria were used to define stroke [14]. Subjects without dementia but with a history of stroke at the baseline examination were included in the analyses.

The association between vascular risk factors and LOAD could be explained by misclassification of VD as LOAD [15]. To address this possible misclassification, we first conducted analyses with possible or probable LOAD as the outcome. We then reclassified persons with possible LOAD deemed to have a contribution from cerebrovascular disease in the consensus conference (mixed dementia) as VD. In both analyses, subjects with types of dementia other than the outcome were censored at the time of dementia diagnosis.

Statistical Methods

Clinical and demographic characteristics were first compared with the presence and absence of diabetes to determine crude associations. Continuous variables were compared using the *t* test, and categorical variables were compared using the χ^2 test.

Cox proportional hazard regression models [16] were used to examine the association between T2D and dementia. Age at dementia onset was the time-to-event variable. We examined 5 outcomes: all dementia, LOAD, VD, LOAD excluding cases with a cerebrovascular contribution, and VD including cases of mixed dementia. A left censoring term for age at baseline was included in all models. The first model adjusted for gender alone, the second model adjusted for gender, ethnic group, education and APOE $\epsilon 4$ allele, and a third model adjusted for additionally hypertension, heart disease, non-HDL cholesterol, HDL cholesterol and history of stroke. The rationale for the first model was adjustment for common demographics. The rationale for the second model was adjustment for LOAD risk factors in our sample. The rationale for the third model was to adjust for theoretical mediators between T2D and LOAD; attenuation of the hazard ratios in this model was interpreted as evidence of mediation, not confounding. We also explored effect modification by APOE $\epsilon 4$ by relating strata of T2D and APOE $\epsilon 4$ to LOAD. SAS for Windows version 9 (SAS Institute, Cary, N.C., USA) was used for all analyses.

Table 1. General characteristics of the study sample: the Washington Heights Inwood Columbia Aging Project 1999–2007

Variable	Values (n = 1,488)
Mean age $\pm$ SD, years	76.0 $\pm$ 6.5
Women	1,001 (67.3)
Black	477 (32.1)
Hispanic	496 (33.9)
White	489 (32.9)
Mean education $\pm$ SD, years	10.9 $\pm$ 4.8
APOE ϵ 4 allele, %	26.1
Diabetes history	253 (17.0)
Stroke history	124 (8.5)
Hypertension history	901 (60.6)
Mean non-HDL cholesterol $\pm$ SD, mg/dl	150.9 $\pm$ 37.0
Mean HDL cholesterol $\pm$ SD, mg/dl	48.3 $\pm$ 14.6
History of heart disease	394 (26.5)
Current smoking	146 (9.9)

Results are means $\pm$ SD as indicated or numbers, with percentages shown in parentheses.

Table 2. Comparison of clinical and demographic characteristics between individuals with and without diabetes

Variable	No diabetes (n = 1,235)	Diabetes (n = 253)	P value
Age $\pm$ SD, years	76.0 $\pm$ 6.6	75.8 $\pm$ 5.8	0.60
Women	831 (67.3)	170 (67.19)	0.98
Black	382 (30.9)	95 (37.6)	0.04
Hispanic	399 (32.8)	97 (39.8)	0.04
White	437 (35.4)	52 (20.6)	<0.0001
Mean education $\pm$ SD, years	11.1 $\pm$ 4.7	9.8 $\pm$ 4.9	<0.0001
APOE ϵ 4 allele ¹	273 (27.6)	37 (18.6)	0.01
Hypertension	712 (57.7)	189 (74.7)	<0.0001
Stroke	94 (7.7)	30 (11.9)	0.02
Mean non-HDL cholesterol $\pm$ SD ² , mg/dl	152.4 $\pm$ 36.8	142.8 $\pm$ 37.3	0.001
Mean HDL cholesterol $\pm$ SD ² , mg/dl	48.9 $\pm$ 14.7	45.2 $\pm$ 13.2	0.001
Heart disease	308 (24.9)	86 (34.0)	0.003
Current smoking	130 (10.7)	16 (6.4)	0.04
All dementia	121 (9.8)	40 (15.8)	0.01
AD	113 (9.2)	36 (14.2)	0.01

Results are means $\pm$ SD as indicated or numbers, with percentages shown in parentheses.

¹ APOE ϵ 4 available in 1,190 participants.

² Non-HDL and HDL cholesterol available in 1,130 participants.

Results

There were 161 cases of dementia in 5,841 person-years of follow-up. There were 149 cases of LOAD and 5 cases of VD. The general characteristics of the sample are presented in table 1.

Compared to persons without T2D, those without T2D (table 2) were more likely to be Black or Hispanic, less likely to be White, had fewer years of education, a lower prevalence of APOE ϵ 4, a higher prevalence of hypertension and heart disease, a lower prevalence of smoking, lower levels of non-HDL cholesterol and HDL cholesterol, and a higher prevalence of all-cause dementia and LOAD.

In multivariable analyses (table 3), T2D was related to a higher risk of all-cause dementia and LOAD after adjustment for age, gender, ethnic group, education and APOE ϵ 4. These associations were attenuated and became nonsignificant after inclusion of vascular conditions and stroke in the model. The analyses relating T2D to VD were limited by small numbers.

In secondary analyses we considered excluded cases with mixed dementia from the definition of LOAD and included them in the definition of VD (table 3). In this analysis T2D was related to LOAD in the model adjusted by age and gender, but was markedly attenuated after including ethnic group, education and APOE ϵ 4 in the model. The main variable driving this attenuation was years of education. There was a strong association between T2D and VD including mixed dementia.

There was no evidence that the relation between T2D and LOAD was modified by APOE ϵ 4 (table 4).

Discussion

In longitudinal analyses on 1,488 subjects from a multiethnic cohort in northern Manhattan, with 5,841 person-years of follow-up, T2D was related to a higher risk of dementia and LOAD.

The mechanisms linking T2D and LOAD are not clear. They may include cerebrovascular and noncerebrovascular mechanisms [17]. T2D is a risk factor for stroke and is accompanied by other stroke risk factors including hypertension and dyslipidemia [18]. Strokes, ascertained by clinical history [19] or as brain infarcts on MRI [20] are related to a higher risk of dementia including LOAD. The mechanisms for this association are not clear. However, pathology studies have demonstrated that the presence of amyloid plaques is lower in brains of persons with

Table 3. Hazard ratios and 95% confidence intervals in parentheses relating T2D and dementia

	Cases	Model 1	Model 2	Model 3
All dementia	161	2.0 (1.4–2.9)	1.7 (1.1–2.7)	1.5 (0.9–2.4)
<i>Analyses with cases of mixed dementia classified as LOAD</i>				
LOAD	149	1.9 (1.3–2.9)	1.6 (1.0–2.6)	1.4 (0.9–2.4)
VD (excluding mixed dementia)	5	1.5 (0.7–13.6)	5.4 (0.3–95.0)	–
<i>Analyses with cases of mixed dementia classified as VD</i>				
LOAD	130	1.8 (1.2–2.7)	1.3 (0.8–2.2)	1.2 (0.7–2.1)
VD (including mixed dementia)	24	3.0 (1.3–7.3)	4.7 (1.6–13.7)	3.7 (1.1–12.6)

Model 1 adjusted for gender; model 2 adjusted for gender, ethnicity, education and APOE ϵ 4 allele; model 3 adjusted for gender, ethnicity, education, ApoE ϵ 4 allele, hypertension, heart disease, non-HDL cholesterol, HDL cholesterol and stroke.

Table 4. Association between strata of T2D and APOE ϵ 4 and LOAD adjusting for age, sex, ethnic group and education

T2D	APOE ϵ 4	LOAD cases	At risk	HR
Absent	absent	60	718	1.0
Absent	present	30	273	1.4 (0.9–2.3)
Present	absent	24	162	1.7 (1.0–2.9)
Present	present	6	37	1.9 (0.7–4.8)

HR = Hazard ratio.

Figures in parentheses are 95% confidence intervals.

dementia who also have infarcts [21, 22], suggesting that the presence of infarcts is an insult that lowers the threshold of amyloid in the brain that is necessary to cause dementia. T2D has been shown in pathology studies to be related to infarcts but not AD pathology in persons with the clinical expression of LOAD [23]. This observation suggests that the main mechanism linking T2D to LOAD clinical expression is the presence of infarcts, which lower the burden of amyloid necessary to cause memory decline and dementia.

The noncerebrovascular mechanisms potentially linking T2D and LOAD include hyperinsulinemia and advanced products of glycosylation. Hyperinsulinemia precedes and may accompany T2D [24]. Insulin can cross the blood-brain barrier [25], and peripheral insulin infusion in the elderly increases 42-amino-acid β -amyloid (A β 42) levels in the CSF [26], a surrogate marker of A β

clearance in the brain and an indirect marker of LOAD risk. There are insulin receptors in the brain including the hippocampus and entorhinal cortex [27], structures affected early in LOAD [28]. Insulin-degrading enzyme (IDE) has been linked to clearance of A β in the brain, and insulin and A β are both competing substrates for IDE [29]. Insulin in the brain can increase the deposition of A β and tau protein phosphorylation, which are central to the pathogenesis of LOAD [25]. A potential pathway is that peripheral hyperinsulinemia downregulates insulin uptake in the blood-brain barrier due to saturation over physiological levels [30]. This may result in reduction of insulin levels in the brain and downregulation of expression of IDE [31] and reduction in IDE-mediated amyloid reduction [29]. This complex observation has been used to support the use of rosiglitazone, an insulin sensitizer [32, 33], and intranasal insulin [34] in the treatment of LOAD. In a T2D environment, diabetic animal and human tissues contain increased advanced products of glycosylation and upregulation of their receptor [35–38]. Increased expression of this receptor is observed in LOAD [39–41].

Numerous prospective studies have shown associations of T2D with cognitive decline [42–44], mild cognitive impairment [44–47], LOAD [6, 48–50] and VD [51, 52]. In general, T2D is related more consistently and more strongly with VD than with LOAD [17]. In our data T2D has a stronger association with VD, but the association with LOAD is also strong, and not explained by a history of stroke. We had shown in our 1992 cohort that T2D was associated with LOAD excluding mixed dementia [6]. In this study we addressed whether the association between

T2D and LOAD was mediated by cerebrovascular disease in 2 ways. First, we included stroke in the models and found partial attenuation of the hazard ratio. Secondly, we reclassified cases of mixed dementia as VD. In this analysis T2D had a strong association with LOAD excluding mixed dementia after adjustment for sex and age, but this finding was markedly attenuated after adjustment for education. Lower education is associated with both LOAD and T2D. It is possible that education is a mediator or confounder in this association. However, it is also possible that we are overadjusting by including education as a covariate. Our findings suggest that the association between T2D and LOAD is at least partially mediated by cerebrovascular disease.

Several epidemiological studies have examined the effect of interactions between APOE $\epsilon 4$ genotype and diabetes or insulin resistance on the risk of LOAD. A longitudinal study on Japanese-American men demonstrated that APOE $\epsilon 4$ increases the risk of LOAD in individuals with T2D, even after adjusting for other vascular risk factors [49]. Meanwhile, other studies found that the T2D and insulin resistance are associated with LOAD independently of the allele status. A cross-sectional study performed in Finland concluded that features of insulin resistance syndrome are associated with AD independently of the APOE $\epsilon 4$ allele [53]. Similarly, diabetes predicted incident LOAD only in individuals without APOE $\epsilon 4$ allele in the Framingham Study prospective cohort [54]. Another longitudinal study observed that diabetes was significantly more common among persons without APOE $\epsilon 4$ than among persons with APOE $\epsilon 4$ [55]. Our findings suggest that the association between T2D and LOAD is not attenuated by APOE $\epsilon 4$.

The main limitations of our study are the ascertainment of T2D and stroke by history. The ascertainment of T2D by history likely missed cases of undiagnosed T2D and resulted in underestimation of the hazard ratios relating T2D and LOAD. In our cohort, a history of stroke has a sensitivity of 32% and specificity of 78% for brain infarcts on MRI [56]. We also could not quantify white-matter hyperintensities (WHI) with brain imaging, and WHI are important vascular predictors of dementia [57] that are prevalent and could mediate the association between diabetes and dementia [58]. However, studies have shown that diabetes predicts dementia independently of WHI [57]. In addition, the assumption that WHI are a proxy of cerebrovascular ischemic disease is uncertain given that WHI could represent neurodegeneration and cerebral amyloid angiopathy [59]. Strengths of our study include the longitudinal nature, and the detailed characterization of LOAD.

Our findings from this cohort recruited in 1999–2001 support our findings from the 1992–1994 cohort and provide further strength to the body of evidence linking T2D to LOAD.

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Disclosure Statement

The authors report no conflicts of interest.

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