

Type 2 Diabetes Is Negatively Associated With Alzheimer's Disease Neuropathology

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Background. In cross-sectional and longitudinal studies, type 2 diabetes has been positively associated with the risk of Alzheimer's disease (AD). The present descriptive study compared diabetic and nondiabetic subjects on the severity of neuritic plaques and neurofibrillary tangles (NFTs) in the cerebral cortex and in the hippocampus.

Methods. The study included specimens from 385 consecutive autopsies of residents of a nursing home (15.8% diabetics). Mean age at death = 84 years [standard deviation (*SD*) = 10], 66% were female, Clinical Dementia Rating mean = 3.0 (*SD* = 1.6), and 32.5% had an APOE4 allele. Additional analyses limited the sample to 268 subjects (14.1% diabetics) without neuropathology other than AD.

Results. Analyses of covariance controlling for age at death, dementia severity (Clinical Dementia Rating score), and APOE4 allele indicated that diabetics had significantly fewer neuritic plaques ($p = .008$) and NFTs ($p = .047$) in the cerebral cortex than did nondiabetics. In the hippocampus, diabetics had significantly lower plaque ratings than did nondiabetics ($p = .019$), but the lower ratings of NFTs did not achieve statistical significance ($p = .082$). In the entire sample, diabetics had significantly less AD-associated neuropathology in all four analyses.

Conclusions. These results raise the possibility that the varied associations observed between diabetes and AD may be specific to as yet ill-defined subgroups of dementia and diabetic patients or may be more characteristic of younger patients than of those who survive to a mean age of 84 years. Future studies are encouraged to examine a variety of other characteristics such as age that may interact with diabetes affecting the incidence of AD.

INTERRELATED biological factors in addition to age can modify the risk, incidence, and potentially the neurobiological features of dementia and Alzheimer's disease (AD). APOE allelic variants have been unambiguously identified as a risk factor for AD (1–3). Several cardiovascular risk factors have been recently associated with the risk of AD (4–6), specifically type 2 diabetes (7,8). Moreover, many of the conditions related to or produced by diabetes, such as advanced glycation end products (AGEs) (9–11) and microvascular pathology (12–14), are increasingly being considered to be risk factors for AD.

Longitudinal population-based studies (7,15–17) and retrospective studies (18) have shown that diabetes is associated with AD and vascular dementias. Other studies have extended this to a relationship between insulin resistance and impaired glucose tolerance with the risk of AD (16,19–21) and cognitive impairment (22). In contrast, there are also clinical and epidemiological studies finding that there is no association between diabetes and the risk of AD (23), that diabetics have a decreased frequency of AD (24), and that the diseases are mutually exclusive (25).

Studying the relationship between diabetes and dementia has the potential for identifying processes that predispose or exacerbate dementia and AD neurobiology and may pinpoint

possible therapeutic avenues. The present study was undertaken to describe the association between diabetes and AD-related neuropathology by comparing the severity of neuritic plaques (NPs) and neurofibrillary tangles (NFTs) in postmortem brain specimens derived from diabetic and nondiabetic subjects.

METHODS

Subjects

Consecutive brain donations from 385 deceased residents of the Jewish Home and Hospital (JHH; Manhattan, NY and Bronx, NY) that were received by Mount Sinai School of Medicine's Department of Psychiatry Brain Bank were studied. All assessments were approved by the JHH and Mount Sinai School of Medicine institutional review boards. Autopsies, after receipt of consent from the legal next of kin, were performed over a period of 17 years. During this period, the autopsy rate has varied between 5 and 30 percent of all deaths. Comparison of cases that consented to autopsy and those that did not has not revealed any specific set of variables that biased the sample in a discernible way.

Research staff reviewed detailed medical records, which were available on all residents, and whenever possible

conducted detailed interviews with staff and family caregivers to obtain information about ante mortem functional and cognitive status. All neuropathological evaluations were performed without knowledge of the donor's medical, cognitive, and functional status. As the objective of this study was to investigate the association between AD neuropathology and diabetes, the primary analyses were limited to subjects with no neuropathology or only AD neuropathology [Consortium to Establish a Registry for Alzheimer's disease (CERAD; 26) categories 1–4: normal brain, definite AD, probable AD, and possible AD, respectively; $n=268$]. Additional analyses were then performed that included subjects with other non-AD-related neuropathological lesions (such as dementia with Lewy bodies, Pick's disease, Parkinson, or cerebrovascular disease including stroke and vascular dementia), or a combination of AD-related and non-AD-related neuropathology (CERAD categories 1–16; $n=385$).

The Clinical Dementia Rating (CDR) scale assesses cognitive and functional impairments associated with dementia and provides specific severity criteria for classifying subjects as nondemented (CDR = 0) or questionably demented (CDR = 0.5), as well as increasing levels of severity of dementia from CDR = 1 to CDR = 5 (27,28). A multistep approach was applied to the assignment of CDR scale scores based on cognitive and functional status during the last 6 months of life (29,30). Briefly, two reviewers independently rated the CDR based on careful review of the subject's medical charts. Subsequently, whenever possible, a phone interview with at least one family member or caregiver was conducted, and a third independent CDR score was assigned. The interrater reliability for 40 subjects undergoing consecutive assessments was high (interclass correlation, 0.88). All CDR scores and chart information were then presented to senior clinicians (DM, VH, KLD, or RCM), and a final consensus CDR score was derived. These neuropathology and cognitive assessment protocols, as well as the formalized procedures for medical chart review have been described extensively (29–32).

Assessment of Diabetes

The JHH maintains extensive medical records on all residents (29,33), with a complete medical history at admission and a complete medical examination (including blood glucose levels) at least yearly. Patients at the JHH were diagnosed as diabetics by a geriatrician or an internist based on the American Diabetes Association criteria [symptoms of diabetes plus causal plasma glucose concentration >200 mg/dL, fasting plasma glucose >126 mg/dL, 2-hour plasma glucose >200 mg/dL during oral glucose tolerance test, and impaired fasting glucose was defined as 110–125 mg/dL (6.1–7.0 mmol/L)]. Diagnoses of diabetes were ascertained from the JHH medical record, but duration and severity of diabetes or the degree of glucose control were not as consistently or reliably available for all patients and were therefore not included in the analysis. The analysis included only subjects with type 2 diabetes or no record of diabetes.

Assessment of APOE Genotype

After DNA isolation from frozen, never-thawed, brain tissue specimens (50 mg) using the Promega Wizard Genomic DNA purification kit (Promega, Madison, WI),

APOE genotyping was performed using a modification of published polymerase chain reaction techniques (34). Participants were categorized as APOE4 positive if they carried at least one copy of the E4 allele, and negative otherwise.

Neuropathological Assessment

The neuropathological assessment procedures used have been extensively described previously (29,30). Standardized representative blocks from superior and mid frontal gyrus, orbital cortex, basal ganglia with basal forebrain, amygdala, hippocampus (rostral and caudal levels with adjacent parahippocampal and inferior temporal cortex), superior temporal gyrus, parietal cortex (angular gyrus), calcarine cortex, hypothalamus with mammillary bodies, thalamus, midbrain, pons, medulla, cerebellar vermis, and lateral cerebellar hemisphere were stained using hematoxylin and eosin, modified Bielschowsky, modified thioflavin S, anti- β amyloid, and anti-tau. Any case showing evidence of Lewy body formation in the substantia nigra or locus coeruleus underwent anti-ubiquitin staining of representative cerebral cortical sections for the identification of cortical Lewy bodies. Neuropathologists were blinded to all clinical and psychometric data while evaluating the slides for the presence and extent of relevant neuropathologic lesions.

Every case was evaluated for the extent of neuropathologic lesions using the CERAD neuropathologic battery (24). Additionally, quantitative data regarding the density of NPs were collected in five cortical areas by using previously published methods (29): the mid frontal gyrus (Brodmann area 9), orbital frontal cortex (Brodmann area 45 and 47), superior temporal gyrus (Brodmann area 21 and 22), inferior parietal cortex (Brodmann area 39), and calcarine cortex (Brodmann area 16). For these quantitative measures of plaque density, five representative high power fields (0.5 mm²) were examined in each cortical region, and an average density score was calculated for each region and expressed as mean plaque density per square millimeter. Only NPs (with and without cores) were included in the NP counts reported here. Two summary variables were derived for statistical analyses: the sum of CERAD ratings (0 = none, 1 = sparse, 3 = moderate, 5 = severe) of NFT densities, and the average of NP densities for the five cerebral cortical regions, in addition to CERAD NFT and NP ratings for the hippocampal formation. Ancillary exploratory analyses revealed that the inclusion of NP and NFT density estimates from the subcortical fields assessed as part of the CERAD neuropathology battery did not substantively contribute to the results described. In addition, previous studies (29,30) had shown that NP and NFT densities in the subcortical regions assessed were not informative with respect to dementia severity.

Statistical Analysis

The primary analyses were limited to subjects with “normal brain” or “definite,” “probable,” or “possible” Alzheimer's disease (CERAD categories 1–4), excluding subjects with other potentially confounding neuropathologies. The diabetic and nondiabetic groups were compared on CDR and age of death by *t* test, and on sex and the presence of APOE4 by Pearson's chi square. Point biserial and phi coefficients are presented as descriptive statistics indicating the correlations

Table 1. Comparison of Nondiabetics and Diabetics on Clinical Dementia Rating (CDR) Score, Age, and Sex

Sample Characteristics	CERAD Neuropathological Categories 1–4*			All CERAD Neuropathological Categories [†]		
	Nondiabetics N = 230	Diabetics N = 38	Statistics	Nondiabetics N = 324	Diabetics N = 61	Statistics
CDR score at death, mean (SD)	3.10 (1.54)	2.59 (1.91)	$t = 1.79; df = 266,$ $p = .074; r_{pb} = -.11$	3.03 (1.61)	2.70 (1.80)	$t = 1.48; df = 383,$ $p = .15; r_{pb} = -.07$
Age at death, mean (SD)	86.10 (9.52)	84.55 (9.94)	$t = 0.92; df = 266,$ $p = .36; r_{pb} = -.06$	84.58 (10.06)	83.20 (10.04)	$t = 0.98; df = 383,$ $p = .33; r_{pb} = -.05$
Post mortem interval, min (SD)	389.4 (506.6)	514.6 (610.4)	$t = 1.40; df = 266,$ $p = .17; r_{pb} = .08$	388.1 (475.3)	428.4 (496.6)	$t = 0.60; df = 383,$ $p = .55; r_{pb} = .03$
% Female	71.7%	65.8%	$\chi^2 = 0.56; df = 1,$ $p = .45; \phi = .05$	66.4%	63.9%	$\chi^2 = 0.13; df = 1,$ $p = .71; \phi = .02$
% 1+ APOE4 allele	31.7%	34.2%	$\chi^2 = 0.09; df = 1,$ $p = .76; \phi = .02$	33.3%	27.9%	$\chi^2 = 0.70; df = 1,$ $p = .40; \phi = -.04$

Notes: *No neuropathology or only AD neuropathology.

[†]All subjects: with no neuropathology, AD-related neuropathology, non-AD-related neuropathology, or a combination of AD-related and non-AD-related neuropathology. CERAD = Consortium to Establish a Registry for Alzheimer's disease (AD); SD = standard deviation.

between these characteristics and dichotomous diabetic status. The cortical summary measures and hippocampal measures of NPs and NFTs in the diabetic and nondiabetic groups were compared by analysis of covariance, controlling for CDR at the time of death, age at death, and presence of APOE4, with correlations presented as descriptive statistics. Analysis of covariance requires that the groups do not differ in their relationships between the dependent variable and each covariate. Tests for heterogeneity of regression coefficients for the covariates were not significant; in particular, there was no interaction between the presence of APOE4 and diabetes. These analyses were repeated for the entire cohort, consisting of cases with normal brains (CERAD category 1), cases classified as AD (CERAD 2–4), and other neuropathologic categories (CERAD categories 5–16).

RESULTS

In the entire study sample, 61 of 385 subjects (15.8%) had been diagnosed with diabetes. Of these 385 subjects, 268 were classified as conforming to CERAD categories of 1–4

consisting of either normal brain (CERAD category 1) or AD with varying levels of neuropathological confidence (definite, probable, or possible AD; CERAD categories 2–4, respectively). Thirty-eight (14.1%) of this no dementia/AD-only (CERAD categories 1–4) subgroup had diabetes. Table 1 provides a breakdown by diabetes versus nondiabetes of CDR, age at death, sex, and APOE-4 status for the entire sample and for the no dementia/AD-only subgroup. The diabetic group did not differ significantly from the nondiabetic group on any of these factors, both in the analyses limited to subjects with CERAD categories 1–4 and the analyses of all subjects.

Table 2 presents comparisons of diabetics and nondiabetics on NP and NFT densities in the cerebral cortex and in the hippocampus, controlling for APOE4, age, and CDR score at death. In the analyses of covariance for CERAD categories 1–4, diabetics had significantly fewer NPs ($F = 7.23; df = 1, 263; p = .008$) and NFTs ($F = 4.00; df = 1, 263; p = .047$) in the cerebral cortex than did nondiabetics. In the hippocampus, diabetics had significantly lower plaque ratings than did nondiabetics ($F = 5.59; df = 1, 260; p =$

Table 2. Comparison of Nondiabetics and Diabetics on Average (SD) Number of NPs and NFTs*

AD Neuropathology	CERAD Neuropathological Categories 1–4 [†]			All CERAD Neuropathological Categories [‡]		
	Nondiabetics	Diabetics	Analysis of Covariance*	Nondiabetics	Diabetics	Analysis of Covariance*
<i>Cerebral Cortex</i>						
N	230	38		324	61	
NPs	11.62 (8.72)	7.48 (8.77)	$F = 7.23; df = 1, 263,$ $p = .008; r = -.16$	9.38 (8.69)	6.02 (8.73)	$F = 7.59; df = 1, 380,$ $p = 0.006; r = -.14$
NFTs	14.65 (7.92)	11.86 (7.96)	$F = 4.00; df = 1, 263,$ $p = .047; r = -.12$	12.31 (8.44)	9.52 (8.47)	$F = 5.57; df = 1, 380,$ $p = .019; r = -.12$
<i>Hippocampus</i>						
N	230	35		324	55	
NPs	1.38 (0.88)	0.99 (0.88)	$F = 5.59; df = 1, 260;$ $p = .019; r = -.14$	1.14 (0.92)	0.79 (.92)	$F = 7.03; df = 1, 374,$ $p = 0.008; r = -.13$
NFTs	2.18 (0.91)	1.90 (0.91)	$F = 3.05; df = 1, 262;$ $p = .082; r = -.10$	1.95 (0.97)	1.65 (0.97)	$F = 4.79; df = 1, 376,$ $p = .029; r = -.11$

Notes: *Controlling for APOE4, Clinical Dementia Rating score, and age at death.

[†]No neuropathology or only AD neuropathology.

[‡]All subjects: with no neuropathology, AD-related neuropathology, non-AD-related neuropathology, or a combination of AD-related and non-AD-related neuropathology.

SD = standard deviation; NP = neuritic plaque; NFT = neurofibrillary tangle; AD = Alzheimer's disease; CERAD = Consortium to Establish a Registry for Alzheimer's disease (AD).

.019), but the lower ratings of NFTs did not achieve statistical significance ($F = 3.05$; $df = 1, 262$; $p = .082$).

The cerebral cortex results were also significant when the analysis was repeated using the entire cohort of 385 cases. Diabetics again had significantly fewer NPs ($F = 7.59$; $df = 1, 380$; $p = .006$) and NFTs ($F = 5.57$; $df = 1, 380$; $p = .019$) than did nondiabetics. Finally, when we examined the hippocampus of the full sample, diabetics had significantly lower ratings of both NPs ($F = 7.03$; $df = 1, 374$; $p = .008$) and NFTs ($F = 4.79$; $df = 1, 376$; $p = .029$) than did nondiabetics.

The results described are based on analyses including subjects pertaining to the CERAD neuropathological category of "normal brain." When the cohort was limited to the subjects with only neuropathological lesions characteristic of AD (i.e., CERAD categories 2–4), similar results, albeit with larger p values reflective of the smaller sample size, were obtained.

DISCUSSION

The present descriptive autopsy study demonstrated significantly fewer cardinal lesions of AD, NPs, and NFTs in the cerebral cortex and in the hippocampus of type 2 diabetic subjects as compared to nondiabetic subjects. Inclusion of all cases (i.e., all subjects irrespective of neuropathological diagnoses), as compared to those with CERAD categories 1–4 only (i.e., no discernable neuropathology or only neuropathology associated with AD), reduced the means of NP and NFT density estimates, as expected, but did not substantially change the observation of reduced AD-related neuropathologic lesions in diabetics relative to nondiabetics. To our knowledge, only two earlier studies (8,35) examined the relationship between Alzheimer's neuropathology and diabetes. Using fewer ($n = 101$) and younger (mean age = 70) subjects, and without controlling for APOE and cognitive or functional level, one study (35), with results consistent with the present results, also found a trend for more Alzheimer's pathology in nondiabetics than in diabetics. In the Honolulu-Asia Aging Study (8), researchers found no relationship between diabetes and AD pathology in the absence of APOE4, but found a higher rate of AD among diabetics when APOE4 was present. In the present study, no interaction between APOE4 and diabetes was found. However, our sample was older and the efficacy of APOE4 as a risk factor for AD appears to diminish with increasing age (36).

Although AGEs are associated with both diabetes (37,38) and AD (9–11), a recent study looking at a specific AGE (N-(carboxymethyl)lysine) (CML) in AD brains found that the extent of CML deposits was inversely correlated with NFT formation, particularly in the hippocampus, consistent with our results. Most of hippocampal pyramidal neurons with NFTs did not have CML deposits, and most of the neurons with heavy CML deposits did not have NFTs (39). The authors concluded that CML deposition does not directly cause NFT formation or neuronal loss in AD.

The results of this study are consistent with the hypothesis that cognitive impairment associated with diabetes reflects factors such as metabolic and microvascular disease in addition to AD neuropathology (37). Current evidence suggests that the neuropathology of dementia, even in persons with AD neuropathology, comprises more than NPs and NFTs, as more than one third of AD patients exhibit vascular and

microvascular pathology and/or degeneration affecting the cerebral endothelium (40,41), which by itself is strongly affected by diabetes (38). Accordingly, another possible explanation of the lower level of AD neuropathology in diabetic subjects, controlling for CDR score, is that cognitive impairment in elderly diabetics is the effect of cerebral microvasculature pathology and its interaction with NPs and NFTs. Nondiabetic subjects with some AD neuropathology could have the same dementia severity as diabetic subjects with less AD neuropathology, but with microvascular impairment.

The advanced age at death of the subjects in this study reflects the increasing proportion of very elderly persons in the population and their high incidence of AD. It should be stressed that we cannot rule out the possibility of a survivor's effect. The population of this study survived until an average age of 85 years. It is possible that diabetic patients who have survived to such an old age have some factor(s) that protect them both from dying and from AD pathology. Put another way, it could be argued that, in general, diabetic subjects with AD do not survive to such an old age and that the population studied here represents a small subgroup in which the deleterious interactions of diabetes and AD are not expressed. Thus, it is possible that diabetes and the risk factors associated with it predispose subjects to greater dementia and greater AD neuropathology, but that other variables or factors associated with longevity counteract this predisposing effect.

Strengths of this study are the relatively large sample sizes used, and measuring AD pathology in diabetics and nondiabetics using systematic and quantitative independent means rather than relying on a clinical diagnosis of AD. Although the diagnosis of diabetes was based on comprehensive blood examinations of the nursing home residents and use of valid, well-known standard criteria, it is possible that diabetes was underdiagnosed and that diabetic patients were not identified either at admission to the nursing home or while there. Because subjects who were formerly hyperinsulinemic become less so in moderate and severe AD (21), they might no longer have been identified as diabetic by the time they entered the nursing home. Lack of identification of diabetes in severely demented patients could lead to a spurious negative association between diabetes and AD. However, the trend level negative association from the similar study (35) presented above was based on a mostly nondemented sample. Another limitation of the study is the lack of information on the duration of diabetes which might be associated with neuropathology of AD. Finally, the autopsy population came from a relatively stable socioeconomic environment, derived from a single institution, and was mostly Caucasian. Although the rates of diabetes differ in various ethnic backgrounds (42), in a comparative pathologic study of AD in brains of East Africans and blacks from Cleveland, Ohio, researchers found no significant differences in their lesions compared with those in whites (43), suggesting that race and ethnic origin are unlikely to have biased the current results unduly.

Although several studies suggest that diabetes increases the risk of dementia and AD, some contradictory findings including the present study diminish confidence in this conclusion and raise the possibilities that associations observed between diabetes and AD may be limited to as yet

ill-defined subgroups of dementia and diabetic patients. Future studies are indicated to examine a variety of other characteristics (for example, age at neuropathological assessment or diabetes-derived central nervous system pathology) that may interact with diabetes affecting the incidence of AD.

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