Increased Risk of Type 2 Diabetes in Alzheimer Disease

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Alzheimer disease and type 2 diabetes are characterized by increased prevalence with aging, a genetic predisposition, and comparable pathological features in the islet and brain (amyloid derived from amyloid β protein in the brain in Alzheimer disease and islet amyloid derived from islet amyloid polypeptide in the pancreas in type 2 diabetes). Evidence is growing to link precursors of amyloid deposition in the brain and pancreas with the pathogenesis of Alzheimer disease and type 2 diabetes, respectively. Given these similarities, we questioned whether there may be a common underlying mechanism predisposing to islet and cerebral amyloid. To address this, we first examined the prevalence of type 2 diabetes in a community-based controlled study, the Mayo Clinic Alzheimer Disease Patient Registry (ADPR), which follows patients with Alzheimer disease versus control subjects without Alzheimer disease. In addition to this clinical study, we performed a pathological study of autopsy cases from this same community to determine whether there is an increased prevalence of islet amyloid in patients with Alzheimer disease and increased prevalence of cerebral amyloid in patients with type 2 diabetes. Patients who were enrolled in the ADPR (Alzheimer disease $n = 100$, non–Alzheimer disease control subjects $n = 138$) were classified according to fasting glucose concentration (FPG) as nondiabetic (FPG <110 mg/dl), impaired fasting glucose (IFG, FPG 110–125 mg/dl), and type 2 diabetes (FPG >126 mg/dl). The mean slope of FPG over 10 years in each case was also compared between Alzheimer disease and non–Alzheimer disease control subjects. Pancreas and brain were examined from autopsy specimens obtained from 105 humans (first, 28 cases of Alzheimer disease disease vs. 21 non–Alzheimer disease control subjects and, second, 35 subjects with type 2 diabetes vs. 21 non–type 2 diabetes control subjects) for the presence of islet and brain amyloid. Both type 2 diabetes (35% vs. 18%; $P < 0.05$) and IFG (46% vs. 24%; $P < 0.01$) were more prevalent in Alzheimer disease versus non–Alzheimer disease control subjects, so 81% of cases of Alzheimer disease had either type 2 diabetes or IFG. The slope of increase of FPG with age over 10 years was also greater in Alzheimer disease than non–Alzheimer disease control subjects ($P < 0.01$). Islet amyloid was more frequent ($P < 0.05$) and extensive ($P < 0.05$) in patients with Alzheimer disease than in non–Alzheimer disease control subjects. However, diffuse and neuritic plaques were not more common in type 2 diabetes than in control subjects. In cases of type 2 diabetes when they were present, the duration of type 2 diabetes correlated with the density of diffuse ($P < 0.001$) and neuritic plaques ($P < 0.01$). In this community cohort from southeast Minnesota, type 2 diabetes and IFG are more common in patients with Alzheimer disease than in control subjects, as is the pathological hallmark of type 2 diabetes, islet amyloid. However, there was no increase in brain plaque formation in cases of type 2 diabetes, although when it was present, it correlated in extent with duration of diabetes. These data support the hypothesis that patients with Alzheimer disease are more vulnerable to type 2 diabetes and the possibility of linkage between the processes responsible for loss of brain cells and β-cells in these diseases. *Diabetes* 53: 474–481, 2004

The islet of Langerhans in type 2 diabetes is characterized by β-cell loss (1,2) and islet amyloid derived from islet amyloid polypeptide (IAPP) (3–5), a protein coexpressed and secreted with insulin by β-cells. Brain dysfunction in Alzheimer disease is characterized by loss of neocortical neurons (6) and focal amyloid deposits, which consist of the locally expressed amyloid β protein (AβP) (7–13). The prevalence of both Alzheimer disease and type 2 diabetes increases with age, and both have genetic components (14–19).

AβP and IAPP both spontaneously form into amyloid aggregates in an aqueous environment (7,8,20,21). The role of these aggregates of IAPP and AβP in β-cell and cortical neuronal death in type 2 diabetes and Alzheimer disease is controversial. Small amyloid aggregates of either of these proteins are cytotoxic (22–25). The mechanism of the cytotoxicity mediated by small protein aggregates has been hypothesized to be by induction of membrane damage (25–27). In the case of IAPP, evidence exists to suggest that abnormal aggregation occurs initially intracellularly, and after cell death, IAPP-derived fibrils accumulate extracellularly (24,28,29). Similar mechanisms are also possible in Alzheimer disease. In vivo, even though IAPP and AβP are present in an aqueous environment, in health neither protein forms fibrils, suggesting that mechanisms

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AβP, amyloid β protein; ADPR, Alzheimer Disease Patient Registry; FPG, fasting plasma glucose; IAPP, islet amyloid polypeptide; IFG, impaired fasting glucose; NFT, neurofibrillary tangle.

exist to prevent this otherwise spontaneous process. These mechanisms likely include the chaperone protein pathway, a system for protein trafficking via intracellular binding proteins (chaperone proteins), which bind nascent proteins and facilitate their transport within the cell (30).

We have previously hypothesized that IAPP amyloid formation in type 2 diabetes may occur under circumstances of genetic variance, which results in a relative decreased affinity of the chaperone protein pathway for trafficking of IAPP (31). It is plausible that a low affinity for binding by one or more chaperone proteins to IAPP may be shared with a similar low affinity for binding to AβP. In support of this hypothesis, Schwartz (32) suggested that there might be a relationship between amyloid deposits in the brain and pancreatic islets.

We used both clinical studies (in living patients and community-based control subjects) and pathological studies to examine the existence of a shared risk for Alzheimer disease and type 2 diabetes. In the clinical studies, we took advantage of a unique community-based (Olmsted County, MN) cohort of well-characterized patients with Alzheimer disease and control subjects without Alzheimer disease (33) to address the question, "Is type 2 diabetes more common in Alzheimer disease?" In the pathology studies, we studied brain and pancreas in autopsy cases from the same community to address the hypotheses *1*) that islet amyloid is more frequent in patients with Alzheimer disease than in control subjects without Alzheimer disease and *2*) that amyloid deposits are more common in the brain in patients with type 2 diabetes than in nondiabetic humans.

RESEARCH DESIGN AND METHODS

Clinical studies

The primary objective of the Mayo Clinic Alzheimer Disease Patient Registry (ADPR) was to acquire a cohort of patients with Alzheimer disease and matched non–Alzheimer disease control subjects for assessment of the progression of Alzheimer disease clinically with respect to imaging and other neurological studies. Patients who were from southeastern Minnesota and had dementia were identified at the time of routine general medical examination in the Department of Community Internal Medicine at the Mayo Clinic. All studies were approved by the Mayo Clinic Institutional Review Board. When there was a suspicion of Alzheimer disease during a routine periodic medical examination, a neurological evaluation that included the Mini-Mental State Exam, Geriatric Depression Scale, Hachinski Ischemic Scale, Short Test of Mental Status, Record of Independent Living, and extensive neuropsychological testing was performed (33). Age- and sex-matched control subjects were randomly identified from the same community clinics. All enrolled cases had detailed evaluation to confirm or rule out (control subjects) Alzheimer disease. Once a patient had been enrolled in the ADPR as a case of Alzheimer disease or as a control, he or she was followed annually for clinical studies that included a fasting blood glucose measurement. Recruitment to the ADPR was haphazard (i.e., not deliberately biased) with respect to the presence or absence of diabetes or the blood glucose concentration. Exclusion criteria were *1*) chronic treatment with glucocorticoids, *2*) a history of pancreatitis, or *3*) type 1 diabetes. The distinction between type 1 and type 2 diabetes was made on conventional clinical criteria. The features favoring type 1 diabetes included lean BMI (and further weight loss) and young age at onset, insulin requirement at onset, documented ketoacidosis, presence of other autoimmune diseases, and a family history of autoimmune disease. Features favoring type 2 diabetes included strong family history, prolonged insulin-independent treatment, obesity, absence of autoimmune diseases, and later age of onset. It is acknowledged that the distinction between type 1 and type 2 diabetes is not without error, but in view of the large number of cases in the present studies and the high prevalence of type 2 versus type 1 diabetes, it is unlikely that the conclusions of the present studies have been influenced by erroneous inclusion of cases of type 1 diabetes (Table 1).

Protocol 1: is type 2 diabetes more common in Alzheimer disease? These recruitment criteria provided a total of 100 patients with Alzheimer disease and 138 non–Alzheimer disease control subjects. In protocol 1, these cases and control subjects were classified according to the criteria of the American Diabetes Association into one of three groups: nondiabetic (< 110 mg/dl), impaired fasting glucose (IFG; 110–125 mg/dl), and type 2 diabetes (>126 mg/dl) based on the most recent glucose concentration measurements. Individuals who were taking blood glucose–lowering treatment for diabetes were classified as type 2 diabetes regardless of their most recent fasting glucose concentration.

TABLE 1
Study cases: clinical studies

	n	Female	Male	Age (years)	BMI (kg/m^2)
Alzheimer disease	100	72	28	78 ± 9	25.5 ± 4.4
Non–Alzheimer disease	138	110	28	79 ± 7	26.8 ± 4.6

Data are means ± SD.

Protocol 2: is the increase in fasting plasma glucose with age greater in Alzheimer disease? We also examined the changes in fasting plasma glucose (FPG) with aging in this cohort of patients. For each subject, we regressed the annual median FPG value against age. This was used to obtain a predicted FPG value for each subject at each decade and also to compare the slopes of the regression lines between groups (Alzheimer disease versus control subjects), using a two-sided rank sum test. To be included in this analysis, patients were required to have FPG values recorded that spanned at least 10 consecutive years from age 50 or greater and at least one value available for each calendar year. Ages of ≥50 years only were considered. These criteria resulted in a study population of 52 patients with Alzheimer disease and 105 non–Alzheimer disease control subjects.

Pathology studies

Case recruitment. Alzheimer disease patients (group 1) and control subjects (non–Alzheimer disease; group 2) had been enrolled in the Mayo Clinic ADPR study during life (33). At death, non–Alzheimer disease and Alzheimer disease cases had an autopsy examination of the brain and the diagnosis of Alzheimer disease (or its absence) was confirmed using CERAD (Consortium to Establish a Registry for Alzheimer Disease) criteria (34). In the pathology study, we include *1*) only cases with clinically and pathologically confirmed Alzheimer disease or non–Alzheimer disease, *2*) cases with an autopsy including both brain and pancreas, and *3*) cases with FPG documented at the Mayo Clinic within 2 years (Alzheimer disease 100%, non-Alzheimer disease 100%) and in most cases 1 year (non–Alzheimer disease 100%, Alzheimer disease 89% of complete autopsies) of death. A mean FPG value for each subject was the mean of at least two independent measurements. Alzheimer disease patients were sex- and age-matched with control subjects during life as per the Mayo Clinic ADPR study and were still matched for age at death (84 ± 8 vs. 85 ± 4 years, Alzheimer disease vs. non–Alzheimer disease; $P = 0.7$). Alzheimer disease was diagnosed 5.5 ± 2.4 (range 1.3–9.9) years before death.

Type 2 diabetes cases (group 3; FPG >126 mg/dl) were identified via Mayo Clinic autopsy records. For inclusion they *1*) had died in the 6 years preceding this study, *2*) were also from Olmsted County, *3*) had an autopsy including both brain and pancreas, and *4*) had had a general medical examination performed including an FPG at Mayo Clinic during the year before death. Exclusion criteria included inadequate preservation of pancreatic tissue for anatomic study, type 1 diabetes, or secondary causes of diabetes. Diagnosis of diabetes in this cohort was 12 ± 9 years before death. These selection criteria yielded 35 cases, but the mean age at death was younger in type 2 diabetes than the in Alzheimer disease cases (73 ± 8 vs. 84 ± 8 years; $P < 0.001$). Therefore, identified from the Mayo Clinic autopsy records was an additional control group consisting of 21 cases (group 4) who were age, BMI, and sex matched with type 2 diabetic patients, had a normal FPG documented within 1 year before death, and were also meeting criteria 1–4 as for group 3. Groups 3 and 4 were included haphazardly (i.e., not consciously biased) with respect to the presence or absence of Alzheimer disease. The characteristics of each of these four study groups are summarized in Table 2.

Protocol 3: is islet amyloid increased in patients with Alzheimer disease? To address this question, we studied pancreas samples obtained at autopsy in 28 cases with Alzheimer disease and 21 without Alzheimer disease (groups 1 and 2 in Table 2). In addition, 35 cases with type 2 diabetes and 21 without type 2 diabetes were studied as a point of reference. Protocol 3 included a total of 105 cases.

Protocol 4: is brain amyloid more common in patients with type 2 diabetes? To address this question, we studied brain samples in 28 cases with and 19 without type 2 diabetes (groups 3 and 4 in Table 2). As a reference, 26

TABLE 2
Study cases: pathology

Group		*n*	Female	Male	Age (years)	Weight (kg)	BMI (kg/m^2)
Pancreas							
1	Alzheimer disease	28	19	9	83.9 ± 7.7	63.5 ± 13.6	24.3 ± 3.4
2	Non–Alzheimer disease	21	12	9	84.8 ± 4.4	70.5 ± 16.8	27.1 ± 6.7
3	Type 2 diabetes	35	15	20	72.7 ± 7.8	83.0 ± 22.9	29.8 ± 6.5
4	Non–type 2 diabetes	21	9	12	72.1 ± 9.1	76.9 ± 11.4	27.2 ± 3.5
Brain							
1	Alzheimer disease	26	18	8	84.2 ± 7.8	62.8 ± 13.5	24.1 ± 3.5
2	Non–Alzheimer disease	19	11	8	84.4 ± 4.3	70.7 ± 17.7	27.4 ± 7.0
3	Type 2 diabetes	28	12	16	72.5 ± 7.8	80.2 ± 21.9	29.5 ± 6.3
4	Non–type 2 diabetes	19	9	10	72.0 ± 9.2	77.0 ± 11.8	27.6 ± 3.4

Data are means ± SD.

cases with Alzheimer disease and 19 without Alzheimer disease were studied. Some paraffin blocks of the superior/midfrontal gyrus were not available, resulting in 92 cases entering protocol 4.

Light microscopy. Pancreas and brain samples were obtained at autopsy from the four groups described above. Slides were examined blinded to the identity of the case by light microscopy.

Pancreas. Sequential sections obtained from paraffin-embedded pancreas tail samples were stained with hematoxylin/eosin and Congo red and by immunostaining for insulin (29). The nature of pink amyloid deposits in Congo red–stained slides was confirmed by green/orange birefringence under polarized light. At least 25 islets per specimen were scored for presence and extent of islet amyloid. The extent of amyloid deposition was classified per islet on a scale from 0 to 4, with 0 = no deposits, 1 = one deposit, 2 = a few small deposits, 3 = major deposition, and 4 = just a few endocrine cells left between confluent deposits.

Brain. Samples of the superior/midfrontal gyrus were collected, and the density of neuritic and diffuse plaques and neurofibrillary tangle (NFT) was determined. For visualizing neurofilaments, paraffin sections of the superior/midfrontal gyrus were stained with a modified Bielschowsky's technique. Per sample, the number of neuritic plaques, diffuse plagues, and NFT was determined in five microscope fields of 2 mm^2 each.

Statistical analysis

Protocols 1 and 2. A rank sum test was used to compare age, and χ^2 tests were used to compare number in groups according to classification for sex and diabetic, nondiabetic, or IFG status. A two-sided rank sum test was used to compare slope of fasting glucose versus age.

Protocols 3 and 4. An unpaired two-tailed Student's *t* test was used to compare age and BMI between groups. The nonparametric Mann-Whitney test was used to compare the frequency and extent of islet amyloid; FPG; and density of neuritic plaques, diffuse plagues, and NFT among groups. The χ^2 test was used to compare the number of Alzheimer disease and non–Alzheimer disease subjects with type 2 diabetes. Spearman rank correlations were used to examine relationships among diffuse plagues, neuritic plaques, and NFT density versus duration of diabetes before death and age at death in type 2 diabetes.

RESULTS

Clinical studies: prevalence of type 2 diabetes and IFG in the living cohort of Alzheimer disease versus non–Alzheimer disease control subjects and trend of FPG with aging

Protocol 1. There was no difference in age or sex distribution between the Alzheimer disease and non–Alzheimer disease control group (Table 1). BMI was slightly but not significantly higher in control subjects versus Alzheimer disease. The prevalence of both type 2 diabetes (34.6 vs. 18.1%; $P < 0.05$) and IFG (46.2 vs. 23.8%; $P < 0.01$) was greater in the Alzheimer disease versus the non–Alzheimer disease control group (Fig. 1); 81% of the Alzheimer disease cases therefore had either type 2 diabetes or IFG.

Protocol 2. When the trend of FPG with aging was examined, there was a gradual increase with aging in both groups ($P < 0.01$ vs. no change). However, the Alzheimer disease group had a greater increase per year compared with non–Alzheimer disease control subjects (0.83 vs. 0.57 mg · dl^{-1} · y^{-1}; $P < 0.01$; Fig. 1). This greater rate of increase of blood glucose was preserved in Alzheimer disease when cases with diabetes were excluded from the analysis.

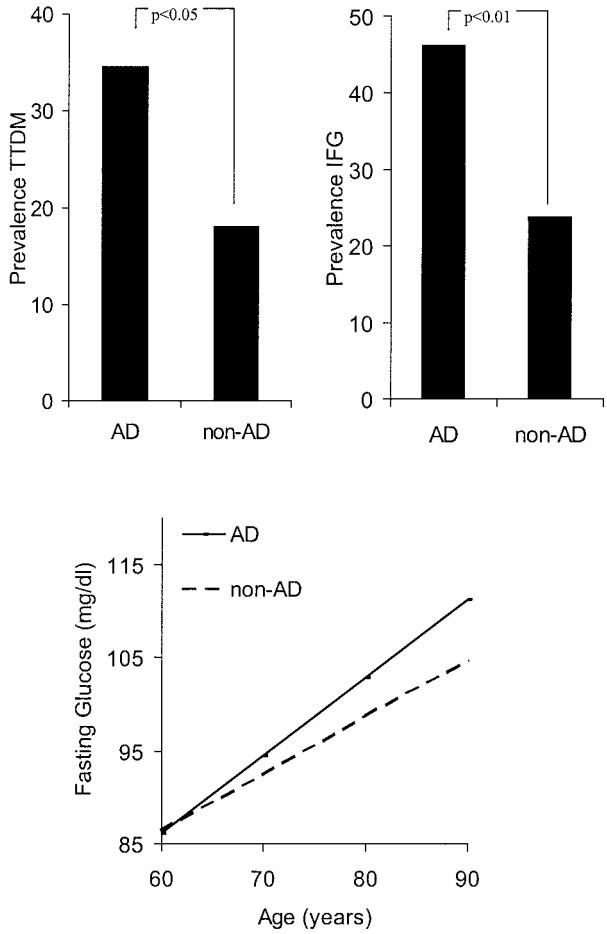

FIG. 1. Protocol 1: the prevalence of diabetes and IFG in the Olmsted County community-based cohort of cases of Alzheimer disease (AD) and control subjects (non–Alzheimer disease [non-AD]; *top*). Protocol 2: the slope of FPG concentration versus age in the same cohort (*bottom*). TTDM, type 2 diabetes.

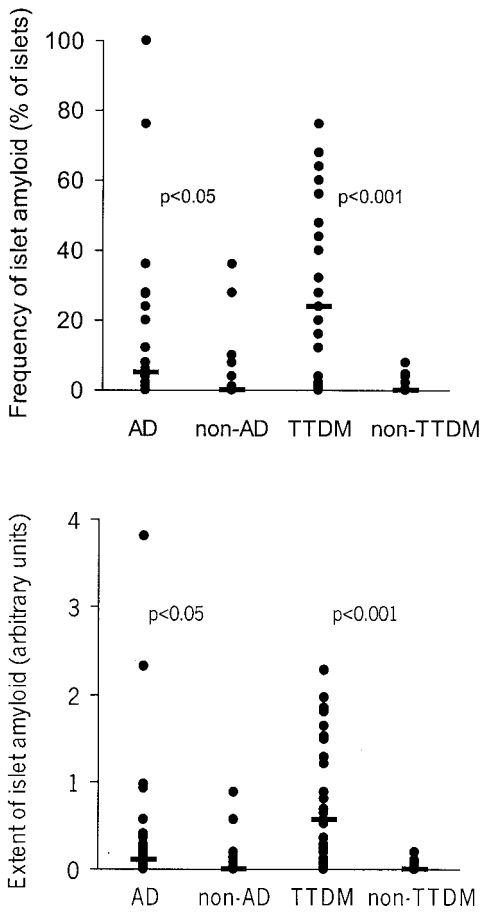

FIG. 2. Protocol 3: frequency of islet amyloid (*top*) and extent of islet amyloid (*bottom*) in patients with Alzheimer disease (AD) and control subjects (non–Alzheimer disease [non-AD]) and in patients with type 2 diabetes (TTDM) and their control group (non-TTDM). Individual values (●) and medians (line).

Pathology studies: islet amyloid in Alzheimer disease (protocol 3) and brain amyloid in type 2 diabetes (protocol 4)

Protocol 3: islet amyloid in Alzheimer disease. Both the frequency and the extent of islet amyloid were higher in the Alzheimer disease group versus the non–Alzheimer disease group (both $P < 0.05$; Fig. 2) despite a trend toward a lower BMI in Alzheimer disease (24.3 ± 3.4 vs. 27.1 ± 6.7 kg/m^2 Alzheimer disease vs. non–Alzheimer disease; $P = 0.06$). As expected, the frequency and the extent of islet amyloid was greater in type 2 diabetes (group 3) versus non–type 2 diabetes (group 4; $P < 0.001$; Fig. 2).

Inclusion of cases in this autopsy protocol was blinded with respect to the presence or absence of diabetes but with the requirement that FPG be documented. Subsequent analysis of the FPG concentrations revealed that the prevalence of type 2 diabetes (FPG >126 mg/dl) in the Alzheimer disease group was 32% and in non–Alzheimer disease cases was 14% ($P = 0.15$). The mean FPG in Alzheimer disease was not higher than in control subjects (126 ± 8 vs. 110 ± 6 mg/dl; $P = 0.09$).

Protocol 4: brain amyloid in type 2 diabetes. The density of diffuse or neuritic plaques or NFT was not different between patients with type 2 diabetes versus nondiabetic control subjects ($P = 0.07$, $P = 0.3$, and $P = 0.4$, respectively; Table 3). As expected, the density of neuritic plaques, diffuse plaques, and NFT was greater ($P < 0.05$) in Alzheimer disease cases (group 1) versus non-Alzheimer disease (group 2).

TABLE 3
Brain pathology

	Median	Range	*P* value
Diffuse plaques			
Type 2 diabetes	0.20	0.0–11.8	0.07
Non-type 2 diabetes	0	0.0–11.6	
Neuritic plaques			
Type 2 diabetes	0	0.0–9.3	0.3
Non-type 2 diabetes	0	0.0–4.8	
NFT			
Type 2 diabetes	0	0.0–1.2	0.4
Non-type 2 diabetes	0	0.0–0.8	

In 22 of 28 type 2 diabetes cases, the year of diagnosis of diabetes was documented. Diffuse plaques were detected in 12 and neuritic plaques in 7 of these 22 cases of type 2 diabetes with a documented age of onset of diabetes. There was a positive relationship between duration of known diabetes and the extent of diffuse plaques ($r_s = 0.8$, $P < 0.001$) or neuritic plaques ($r_s = 0.9$, $P < 0.01$) in these cases (Fig. 3). In contrast, in neither type 2 diabetes nor non–type 2 diabetes was there a correlation with the density of either of these plaques and the age at death.

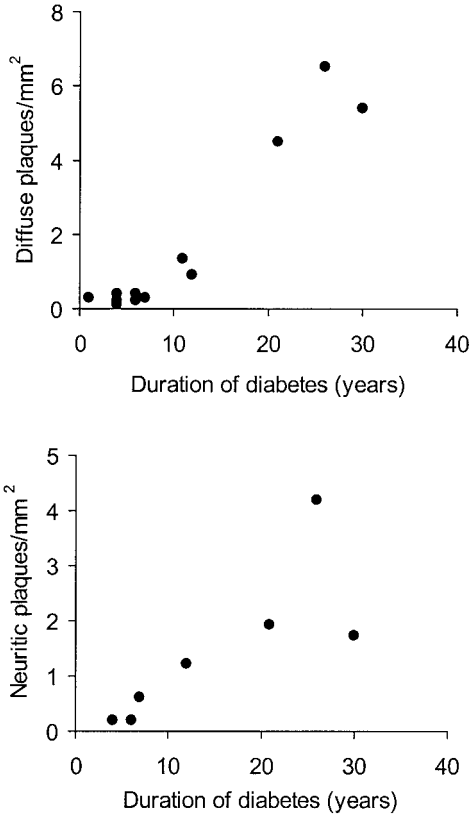

FIG. 3. Protocol 4: relationship between the density of diffuse plaques ($r_s = 0.8$, $P < 0.001$; *top*) or neuritic plaques ($r_s = 0.9$, $P < 0.01$; *bottom*) versus the duration of diabetes in patients with type 2 diabetes. Cases were included only when the duration of diabetes was documented and the respective plaque type was detected (y did not equal zero).

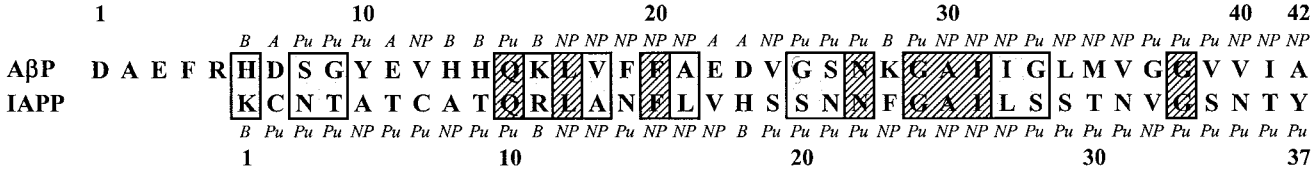

FIG. 4. The structural overlap between IAPP and AβP. There is a major overlap (~90%) in the structural properties of $IAPP_{20–28}$ and $AβP_{25–33}$ when the amino acids are classified as acidic (A), basic (B), nonpolar (NP), and polar uncharged (Pu). Gray boxed and hatched areas are identical amino acids; gray boxed areas are amino acids with similar structural properties.

DISCUSSION

We report that the prevalence of both type 2 diabetes and IFG are increased in a well-characterized community cohort of patients with Alzheimer disease from southeast Minnesota. In the related pathology studies, we also report an increased frequency of islet amyloid in patients with Alzheimer disease**.** However, brain amyloid was not increased in patients with type 2 diabetes versus non–type 2 diabetes, but the density of diffuse and neuritic plaques, when present, was associated with the duration of diabetes.

The studies were initially undertaken to test the hypothesis that there may be a shared predisposition for development of islet amyloid and brain amyloid in patients with Alzheimer disease and type 2 diabetes, respectively. This postulate arose from the close resemblance in pathology in the brain in Alzheimer disease and islets in type 2 diabetes. In both diseases, a locally expressed protein (AβP in Alzheimer disease and IAPP in type 2 diabetes) is deposited in amyloid deposits with a gradual decline in the number of cells of the respective proteins. Amyloid deposits of both AβP and IAPP (or more likely their oligomeric precursors) are cytotoxic (22,23,35–40) by a mechanism that may relate to membrane disruption (25–27). However, as yet, there is still no clear explanation for why these amyloidogenic proteins form amyloid fibrils in those who develop type 2 diabetes and Alzheimer disease. Because both of these proteins spontaneously form amyloid fibrils in vitro in the aqueous environment present in the cell, mechanisms must exist in health to prevent this aggregation, which presumably include the chaperone protein pathway (30). All newly synthesized proteins are bound by a chaperone protein that has the function of preventing insoluble proteins (e.g., IAPP and AβP) from aggregating in cells and trafficking the protein to its appropriate subcellular location. Chaperon proteins have been described as promiscuous because each chaperone protein binds and traffics numerous different proteins with structurally similar properties (30). As individual chaperone proteins traffic structurally similar peptides, it is possible that IAPP and AβP share one or more chaperone proteins. In Fig. 4, the amino acid sequence and structural properties of each amino acid of $IAPP_{1–37}$ and $AβP_{1–42}$ are shown. They have been aligned to reveal the major overlap (~90%) in structural properties of $IAPP_{20–28}$ and $AβP_{25–33}$, areas that are hydrophobic and therefore likely to be a target for binding by chaperone proteins. Furthermore, this region of IAPP is well-established as the amyloidogenic sequence (36) and $AβP_{25–35}$ is neurotoxic (41). Recently it has been suggested that the toxic intermediate form of IAPP and AβP oligomers are recognized by the same antibody, suggesting a strong structural relationship (42).

If the chaperone protein pathway for trafficking AβP or IAPP is shared, then any decreased capacity for trafficking of either might also be shared. Under these circumstances, aggregation of either or both proteins might occur, resulting in the development of the relevant phenotype for Alzheimer disease and/or type 2 diabetes. In addition, type 2 diabetes and Alzheimer disease increase in prevalence with aging, and cell chaperone protein capacity declines with aging (43), which would be expected to reveal any partial deficiency in chaperone capacity with aging. Therefore, one potential explanation for the reported shared risk for Alzheimer disease and type 2 diabetes and similar pathology is that IAPP and AβP share one or more chaperone proteins and that a functional defect in this shared pathway (decreased chaperone protein binding, decreased chaperone protein availability) results in a shared vulnerability for AβP to aggregate in β-pleated sheets in cortical cells and IAPP to aggregate in β-cells.

An alternative hypothesis to account for the reported overlap between islet amyloid and brain amyloid is that subtle hyperglycemia causes Alzheimer disease. This possibility has been reviewed by Finch and Cohen (44). Finch and Cohen proposed that the progressive increase in plasma glucose concentration that occurs with aging in the general population may be important in the pathogenesis of Alzheimer disease. They proposed that this may be mediated by induction of oxidative stress or by glycosylation of key regulatory proteins (45,46). The current study was at least partly supportive of this interesting hypothesis. When present, the density of diffuse and neuritic plaques in brain increased with the duration of diabetes but not with age. Prolonged exposure to hyperglycemia thus might trigger brain plaque formation in those at risk. However, against this hypothesis, there was not an overall increase in the pathological features of Alzheimer disease in cases of type 2 diabetes compared with control subjects, consistent with a previous pathological report (47).

The high risk of underlying vascular disease in diabetes has been reported to increase rates of vascular dementia in diabetes (48,49). Furthermore, hypertension and hyperlipidemia, both strongly associated with diabetes (50), both are risk factors for vascular dementia (51–54). Another potential mechanism for decreased cognitive function in long-standing diabetes is recurrent hypoglycemia (55–57). However, in the present studies, we included only cases with type 2 diabetes in which recurrent hypoglycemia is rare in comparison with type 1 diabetes.

These multiple factors that might influence a relationship between dementia and type 2 diabetes as well as

differences in populations and inclusion criteria likely contribute to the conflicting epidemiological data in this field. Some studies suggest that the prevalence of Alzheimer disease is increased in type 2 diabetes (58–60), whereas in others, it has been reported as decreased (61–66) or comparable (48,49,67–71). A confounding factor in these studies (including the current one) is that Alzheimer disease is often accompanied by a decreased BMI presumed to be a result of decreased food intake. Because the most potent risk factor for development of type 2 diabetes is an increased BMI, it is possible that an association between these conditions has been obscured by the relative protective effect of a decreased BMI in Alzheimer disease. Alternatively, it is possible that people with Alzheimer disease exercise less and therefore have decreased insulin sensitivity and increased risk for type 2 diabetes. As type 2 diabetes tends to develop at a younger age than Alzheimer disease and is associated with a decreased life expectancy, early death from complications of diabetes might obscure subsequent development of Alzheimer disease. The current pathology studies are unique inasmuch as the Alzheimer disease and non–Alzheimer disease groups were fully characterized both in life and by autopsy, and so although the numbers are small, it is provocative that there is a distinct increase in risk of islet amyloid in patients with Alzheimer disease despite a lower BMI. The clinical data (protocols 1 and 2) are also community-based cases that have been defined extensively with respect to the presence or absence of dementia and followed over a relatively long term (33). It is of interest that a population-based study from the same region showed an association between type 2 diabetes and Alzheimer disease (59). Whereas the former study examined records of all known cases of type 2 diabetes in the Rochester area at the time of the study for a diagnosis of dementia and Alzheimer disease (1,455 cases), the present study was focused on a much smaller cohort of patients with Alzheimer disease (100 cases) and control subjects (138 cases) enrolled in the ADPR (33), wherein the diagnosis of Alzheimer disease was rigorously established, and then the same patients were followed annually in the study thereafter and when deceased were included in the autopsy studies. One other factor that might have caused discrepancies between reported studies is the changing definition of diabetes. The present study uses the criteria adopted for FPG concentrations in 1997 by an expert committee convened by the American Diabetes Association (72). As a consequence of this report, the plasma glucose concentration required to establish the diagnosis of diabetes was decreased from 140 mg/dl to 126 mg/dl. Furthermore, a high-risk group was established for the subsequent development of diabetes with an FPG concentration of 110–125 mg/dl. Studies that used the higher values for diagnosis of diabetes would report lower prevalence rates in both Alzheimer disease and control subjects and possibly not observe differences between groups that might be evident with the criteria used here.

Another potential confounding factor in previous as well as the present studies is recruitment bias. All studies performed at major tertiary referral centers such as the Mayo Clinic are subject to such bias. Efforts were made to minimize this in the present clinical studies by recruitment of patients from the local community from the community clinics of the Mayo Medical Center. Patients were therefore attending the Mayo Clinic community clinics for primary care when they were recruited for either the Alzheimer disease or control groups of the clinical studies. Nonetheless, other recruitment bias may be introduced in a study such as ours by the failure of affected patients to seek medical care and therefore be unavailable for consideration. In the present study, there is a greater proportion of women than men in the clinical studies, which might be in part a reflection of recruitment bias but also potentially be due to the shorter life span of men than women once Alzheimer disease is diagnosed. Autopsy studies of Alzheimer disease cases and control subjects (for islet amyloid) would be subject to the same ascertainment bias as the ADPR since the cases were in the ADPR until death. In autopsy studies of type 2 diabetes cases versus control subjects for brain amyloid, we sought to minimize deliberate bias by including most recent autopsies in reverse sequence from cases that were appropriate for inclusion for these criteria. People who have an autopsy are of course in themselves a subgroup of the general population, so bias has to be considered. Notwithstanding these limitations, we do have the opportunity of presenting autopsy data from cases that were well characterized in life compared with most autopsy studies.

In conclusion, we report that there is an increased prevalence of both type 2 diabetes and IFG in a community cohort of patients with Alzheimer disease followed in Olmsted County, Rochester, Minnesota. We also report increased islet amyloid in patients with Alzheimer disease compared with control subjects. However, we did not observe an increased frequency of brain amyloid in cases of type 2 diabetes, although in cases of type 2 diabetes that did have brain amyloid, the extent of this amyloid increased with longer duration of diabetes, a correlate that did not extend to the age of patients with type 2 diabetes. Taken together, these clinical and pathological studies support a possible link between the neurodegenerative processes that lead to loss of cortical brain cells in Alzheimer disease and the loss of β-cells in type 2 diabetes.

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