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Type II Diabetes in Mild Cognitive Impairment and Alzheimer's Disease: Results from a Prospective Population-Based Study in Germany

Pablo Toro, Peter Schönknecht and Johannes Schröder*
Section for Geriatric Psychiatry, University of Heidelberg, Heidelberg, Germany

Abstract. Diabetes mellitus type 2 (T2DM) is considered to be an important risk factor for mild cognitive impairment (MCI) and subsequent Alzheimer's disease (AD). The majority of studies relating T2DM to MCI and AD were performed in North America. We investigated the potential impact of T2DM on the development of MCI and AD in the Interdisciplinary Longitudinal Study on Adult Development and Aging which involves a representative birth cohort of subjects born between 1930 and 1932 in Germany. Subjects received a thorough psycho-geriatric examination and neuropsychological testing; particular care was taken to exclude subjects with severe medical or neurological conditions sufficient to explain the cognitive deficits, or other major psychiatric disorders. When compared to healthy subjects ($n = 159$), patients with MCI ($n = 108$) or AD ($n = 26$) showed a tendency towards increased prevalence rates for T2DM (16% vs. 23%; $\chi^2 = 1.7, p = 0.18$). In both patients with MCI and controls, T2DM was associated with psychomotor slowing but not deficits in other cognitive domains typically involved in MCI. Our findings indicate that T2DM is involved in MCI and may aggravate the clinical picture as a concomitant factor.

Keywords: Aging-associated cognitive decline, Alzheimer's disease, diabetes mellitus, Interdisciplinary Longitudinal Study on Adult Development and Aging, mild cognitive impairment

INTRODUCTION

Diabetes mellitus type 2 (T2DM) is not solely an important health problem in the United States and throughout the western world, but is considered to be an important risk factor for mild cognitive impairment (MCI) and subsequent Alzheimer's disease (AD). In Germany, the prevalence of T2DM is rising: while in a 1998 survey, the prevalence over all ages was at 5.9%, it reached 7.9% in 2004 [1]. For people over the age of 60, T2DM prevalence rates are estimated to range between 18 and 28%, reflecting the importance of this disease in the young old. Although the relationship between T2DM, hyperinsulinemia, and dementia has been addressed in a number of studies (for a review see [2]), most of them used samples comprising a wide range of age (i.e., 60–75 years) and showed divergent findings: some relating T2DM to AD and MCI [3–5] and others finding no association or only an association with vascular dementia (VaD) [6–8].

On basis of these epidemiological findings, a number of factors – hyperinsulinemia, advanced glycation end products, adipokines and cytokines, and vascular risk factors – were hypothesized linking T2DM and AD [2,9]. The former three refer to pathophysiological changes supposed to directly interfere with the metabolism of amyloid-β. Hence, one may expect that these changes should aggravate the clinical picture of MCI or AD. The potential impact of vascu-

*Corresponding author: Prof. Dr. med. Johannes Schröder, Section of Geriatric Psychiatry, University of Heidelberg, Voßstr. 4, 69115 Heidelberg, Germany. Tel.: +49 6221 56 5468; Fax: +49 6221 56 5327; E-mail: johannes.schroeder@med.uni-heidelberg.de.

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lar risk factors and the respective changes in amyloid-β metabolism is not yet fully understood. However, these changes may pose rather global effects on cerebral functioning which not only apply for MCI or AD but can affect T2DM patients in general. One way to test this hypothesis in a clinical study is to compare patterns of neuropsychological functioning in patients with MCI or AD and healthy controls with and without T2DM. If T2DM had specific effects on MCI and AD, it should aggravate the typical neuropsychological deficits. Alternatively, global effects of T2DM should lead to rather unspecific neuropsychological changes which strike all patients with T2DM irrespective of a potential cognitive diagnosis.

Symptomatic cognitive deficits due to severe medical or neurological diseases, or mild cognitive disorder (MCD) according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria, have to be considered as an important potential confounding variable. Patients suffering from typical medical complications of diabetes secondary to an advanced micro- and macro-angiopathy as proliferative retinopathy, peripheral neuropathy, and peripheral vascular disease fall into this category.

In the present study, we investigated the potential impact of T2DM on the development of MCI and AD in the Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE) which involves a representative birth cohort of subjects born between 1930 and 1932 in Germany. The aim of our study was: 1) to confirm and enhance the epidemiological findings on the association between T2DM, MCI and AD; and 2) to investigate the question whether T2DM is directly involved in the pathogenesis of the disease or acts as a concomitant factor.

METHODS

Subjects

The ILSE is a prospective study on adult development in Germany based on two birth cohorts born in 1930–1932 and 1950–1952 [10]. Participants were randomly identified and recruited according to community registers which are compulsory for any citizen aged 16 and above in Germany; this recruitment procedure yielded an almost representative sample for the respective communities. Subjects have been followed up since 1993/94 for at least 13 years. The present study is based on the results of 381 participants from the 1930–1932 birth cohort who completed the 3rd examination wave at an average age of 75 years.

The participants were carefully screened for physical and mental health by extensive interviews, physical examination and laboratory tests including cholesterol, triglycerides and glycosylated hemoglobin (HbA_{1c}) performed by a physician. In addition, potential psychiatric disorders were assessed clinically and by using the German version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) [11]. The study was approved by the ethics committee of the University of Heidelberg. After complete description of the study to the subjects, written informed consent was obtained.

Severity of cognitive deficits was assessed by the Mini-Mental State Examination (MMSE) [12]. In addition, the subtests logical memory I and II of the Wechsler Memory Scale (WMS), German version [13] and the Trail Making Test (TMT) [14] were applied to address memory and learning, and attention and cognitive flexibility, respectively (a detailed description of the neuropsychological test battery used is given elsewhere [15]).

Diagnostic categories

MCI was diagnosed according to the aging-associated cognitive decline (AACD) criteria as described elsewhere [16]. MCD was diagnosed using ICD-10 criteria, respectively (for details see [15]). For the diagnosis of AD and VaD, the NINCDS-ADRDA and the NINDS-AIREN criteria were applied [17,18]. All diagnoses were the result of a consensus conference of two specialists in psychiatry under supervision of a specialist in Old Age Psychiatry. The diagnosis of diabetes was established by history taking, clinical examination and laboratory data. Moreover, the patient's family physician was contacted if information was incomplete.

Statistics

SAS software (version 9.01; SAS Institute, Cary, NC, USA) was used for all statistical analysis; p-values less than 0.05 were considered significant. Analyses of variance with post hoc Duncan's tests were calculated in order to compare the demographic and clinical data between the diagnostic groups. Gender and diabetes distributions were analyzed by the χ^2-test.

Table 1
Demographic and clinical characteristics of the diagnostic groups

Mean ± SD/ **n** (%)	Controls (A)	MCI (B)	AD (C)	Duncan or χ^2
n	159	108	26	
age	74.2 ± 1.1	74.4 ± 1.1	75.0 ± 1.2	n.s.
Female sex	78 (49.1)	53 (49.1)	10 (38.5)	n.s.
Education years	13.6 ± 2.3	12.3 ± 2.2	11.7 ± 2.3	A>B, C
T2DM	27 (17.0)	25 (23.2)	6 (23.1)	n.s.
T3 MMSE	28.9 ± 1.2	28.0 ± 1.4	24.1 ± 2.5	A>B>C
T3 WMS I	25.1 ± 5.1	17.4 ± 4.6	10.7 ± 4.7	A>B>C
T3 WMS II	22.2 ± 4.9	12.8 ± 4.3	6.2 ± 3.8	A>B>C
T3 TMT A†	33.7 ± 11.0	42.1 ± 15.4	67.5 ± 48.6	A<B<C
T3 TMT B†	93.6 ± 30.5	131.6 ± 48.9	181.1 ± 61.3	A<B<C

Abbreviations: T2DM, Diabetes mellitus type 2; MMSE, Mini-Mental State Examination; WMS, Wechsler Memory Scale; TMT, Trail making test; SD, standard deviation.
†TMT in seconds.

Table 2
Effects of a concomitant T2DM with the results of a multivariate analysis of variance

Mean ± SD	MCI		Controls		Main effect diagnosis	Main effect diabetes	Interaction diagnosis*diabetes
	T2DM+ $n = 25$	T2DM− $n = 83$	T2DM+ $n = 27$	T2DM− $n = 132$			
HbA_{1c}	6.6 ± 0.8	5.7 ± 0.5	6.9 ± 1.1	5.7 ± 0.4	F = 1.61	F = 67.41***	F = 1.09
Education years	12.6 ± 2.3	12.1 ± 2.2	13.7 ± 2.5	13.5 ± 3.1	F = 8.32**	F = 0.57	F = 0.20
MMSE	28.2 ± 1.2	27.9 ± 1.4	28.9 ± 1.0	28.9 ± 1.3	F = 14.30**	F = 0.46	F = 0.28
WMS I	17.3 ± 3.9	17.4 ± 4.8	25.5 ± 4.4	25.0 ± 5.3	F = 94.05***	F = 0.05	F = 0.11
WMS II	13.0 ± 4.7	12.8 ± 4.2	22.6 ± 3.9	22.0 ± 5.1	F = 147.79***	F = 0.22	F = 0.09
TMT A†	46.0 ± 23.0	40.9 ± 12.2	36.9 ± 16.8	33.0 ± 9.3	F = 15.34**	F = 4.37*	F = 0.08
TMT B†	142.2 ± 50.6	128.3 ± 48.3	104.2 ± 33.0	91.4 ± 29.7	F = 33.56***	F = 4.25*	F = 0.01

Abbreviations: T2DM, Diabetes mellitus type 2; MMSE, Mini-Mental State Examination; WMS, Wechsler Memory Scale; TMT, Trail making test; SD, standard deviation; HbA1c, glycosylated hemoglobin.
$*p < 0.05$; $**p < 0.005$; $***p < 0.0001$.
†TMT in seconds.

RESULTS

Of the 500 subjects initially recruited from 1993 to 1994, 381 (76.2%) were reassessed at the 3rd examination wave. T2DM was diagnosed in 77 (20.2%) of the subjects in at least one of the three examination waves. No subject had a diagnosis of diabetes type I; subjects who met criteria for other mental disorders such as major depression, anxiety disorders or MCD were not included in the analysis, leaving a sample of 293 persons. Of these remaining subjects, 26 were diagnosed with AD, 108 with MCI, and 159 with no mental disorders.

Demographic and clinical characteristics of the diagnostic groups are shown in Table 1. There were no significant differences with respect to mean age of subjects or gender distribution. Mean school education years was significantly higher ($F = 10.59$, $p < 0.0001$) in the control group than in patients with MCI or AD. The percentage of subjects with diabetes was higher in patients (23.2% in MCI and 23.1% in AD) than in controls (17.0%); however, this difference did not reach significance level ($\chi = 1.73$, df $= 2$, $p = 0.42$). Since the prevalence rates of T2DM were similar in both patients with MCI and AD, they were merged into a single group of subjects with MCI or AD. Again, significant differences in T2DM prevalence rates did not arise ($\chi = 1.73$, df $= 1$, $p = 0.18$). As expected, mean MMSE scores differed significantly among all three groups ($F = 110.57$, $p < 0.0001$) with the MCI group ranking in between AD patients and controls. Accordingly, WMS I ($F = 123.34$, $p < 0.0001$), WMS II ($F = 183.65$, $p < 0.0001$), TMT A ($F = 30.32$, $p < 0.0001$), and TMT B ($F = 49.22$, $p < 0.0001$) were best accomplished by the controls and least by the AD patients.

In Table 2, the MCI and the control group were classified according to the presence or absence of T2DM. Multivariate analyses of variance yielded significant main effects for "cognition" in all variables under investigation except HbA1c ($1.61<F<147.71$), whereas the main effect "T2DM" were significant for HbA1c and performance in the TMT A and TMT B ($0.05<F<67.41$) only. The interaction "cognition * di-

abetes" did not reach significance level for any of the variables included ($0.01<F<1.09$).

DISCUSSION

The present study yielded two major findings: 1) support for a somewhat increased prevalence rate of T2DM in MCI and AD although this difference did not reach significance level; and 2) an indication that T2DM may lead as a concomitant disorder to psychomotor slowing and impaired cognitive flexibility in patients with MCI as well as controls.

As to be expected, neuropsychological performance differed between the diagnostic groups with AD patients followed by those with MCI showing significant deficits when compared to the healthy controls. The former groups were also characterized by a lower educational level as a putative surrogate of cognitive reserve [19].

The slight increase of prevalence rates for T2DM in both patients with MCI and AD corresponds with the studies published by Luchsinger 2007 and Ott 1999 which reported a significant increase on the basis of large population samples recruited in northern Manhattan and Rotterdam. Whereas similar prevalence rates between 20 and 30% for T2DM were reported for patients with MCI and AD, rates obtained among the controls varied considerably from 10.5% [5] to 17.0% in the present study and 21.6% [4]. The overall T2DM prevalence rate of 20.2% obtained in the present study is well in the range reported for this age group in the German population. From these data, one may conclude that the negative results of our study are likely to be accounted for by the sample size. However, an Italian study [8] also reported slightly but not significantly increased prevalence rates for T2DM in a sample of 2963 participants recruited from the general population. Along with this, the Canadian study of health and aging described a significant association for VaD but not AD [6], whereas Luchsinger could confirm an increased T2DM prevalence neither for AD nor for "non dementia cognitive impairment without stroke" after controlling for apolipoprotein $\varepsilon 4$ status [7]. Obviously, these discrepancies may refer to methodological issues, such as the use of different diagnostic categories or the consideration of co-morbidity with psychiatric diseases. The majority of studies used Petersen's MCI criteria for clinical diagnosis; however, the validity of the AACD criteria applied in the present investigation is underlined by the finding of similar T2DM prevalence rates in patients with MCI and AD. Co-morbidity with other major psychiatric disorders, in particular major depression, was not addressed although the former can be associated with T2DM and related conditions. Therefore, particular care was taken to exclude subjects with a history of major psychiatric diseases such as major depression or substance abuse in the present study.

In a second step, potential effects of T2DM as a concomitant disorder were examined by analyzing its potential impact on the neuropsychological performance. A significant diabetes effect was restricted to the attention-concentration task TMT A and the cognitive flexibility test TMT B both of which share a psychomotor component. In contrast, those neuropsychological domains typically affected in early AD or MCI, i.e., memory or learning were not affected by diabetes. The same applied for global cognitive performance as measured by the MMSE. This double dissociation suggests that T2DM may act as a concomitant disorder affecting psychomotor speed rather than other cognitive domains typically involved in AD.

Since the treatment of diabetes is covered by the social system in Germany, and all ILSE participants with T2DM were assisted (medically and/or by a nutritionist) in achieving good glucose control, the T2DM effect on cognition is probably well balanced and minimized in the present sample as suggested by the low HbA_{1c} blood levels observed in the T2DM group. Moreover, patients with MCD, i.e. those suffering from somatic diseases sufficient to impair cognition including patients with the typical clinical complications of T2DM such as proliferative retinopathy, peripheral neuropathy, and peripheral vascular disease, were excluded. A similar pattern of neuropsychological deficits with psychomotor slowing but sparing of mnestic abilities was consistently described by Ryan and colleagues in otherwise healthy patients with T2DM when compared to controls [20]. They suggested a "central neuropathy" which would be probably induced by chronic hyperglycemia; while psychomotor slowing was best predicted by the presence of clinically significant biomedical complications its pathogenesis and why other cognitive skills are relatively unaffected remains poorly understood.

In conclusion, our findings conform with an effect of T2DM on MCI and AD as emphasized in recent studies. The question if T2DM is directly involved in the pathogenesis of AD and MCI as its putative preclinical state or complicates the clinical condition of patients as a concomitant disorder needs to be investigated further.

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