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Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes mellitus

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Abstract

Background: exact mechanisms underlying cognitive dysfunction in diabetes mellitus (DM) remain unclear. Imaging studies of the brain could help to identify possible structural brain lesions underlying cognitive dysfunction.
Objective: to describe a detailed neuropsychological profile in patients functioning independently with type 2 DM. Secondly, correlations were studied between cognitive impairment and brain lesions on magnetic resonance imaging (MRI), i.e. periventricular hyperintensities (PVH), deep white matter lesions (DWML), medial temporal lobe atrophy (MTA), cerebral atrophy and lacunar infarcts. In addition, the influence of relevant disease variables of DM was studied.
Methods: 92 patients with type 2 DM (mean age 73.2 ± 5.7 years, mean duration 13.8 ± 10.8 years) and 44 control subjects (mean age 72.9 ± 5.3 years) were included and underwent an extensive neuropsychological test battery and an MRI of the brain.
Results: neuropsychological scores were worse for each cognitive domain except for memory functions after adjustment for hypertension in a group of elderly patients with type 2 DM compared to healthy control subjects. Only PVH were independently associated with motor speed, whereas all other MRI measures were not independently associated with cognitive impairment. Interactions between the different MRI measures were not present. Glycosylated haemoglobin (HbA_{1c}) and duration of DM were significantly associated with cognitive dysfunction.
Conclusions: the data of this cross-sectional study show that type 2 DM is associated with diminished cognitive function in different cognitive domains, while memory is less affected after adjustment for hypertension. The association of cognitive impairment with MRI measures is equivocal, whereas HbA_{1c} and duration of DM were significantly associated with cognitive dysfunction.

Keywords: *diabetes mellitus, cognition, magnetic resonance imaging, elderly*

Introduction

Type 2 Diabetes Mellitus (DM) is a common condition in the elderly and has been associated with cognitive impairment and dementia [1–4]. The majority of studies investigating cognitive impairment associated with type 2 DM had a case–control design and indicated that older DM patients perform worse than controls on a variety of cognitive function tests. Cognitive impairment may particularly affect verbal memory or complex information processing in type 2 DM [1, 3]. However, study populations were mostly small and the studies did not take into account possible differences

in educational level and usually did not adjust for age, sex and comorbid hypertension [3]. In addition, most studies did not perform an extensive neuropsychological test battery and population studies more often used global cognitive screening tests like the Mini Mental State Examination (MMSE) [3, 5].

The cerebral mechanisms underlying these cognitive deficits and the responsible brain structures remain to be delineated and are the subject of intense research, but brain atrophy and vascular changes have both been assumed [6, 7]. Although a significant relation between DM and cortical or subcortical atrophy has been found in several studies, the results with regard to the relation of DM and white matter lesions (WML) or lacunar infarcts are conflicting [8–16]. These inconsistencies may be due to methodological problems, like the number of patients studied, the use of insensitive rating scales to assess WML or patient selection. In all the studies no associations between cognitive impairment and brain imaging abnormalities in diabetic patients were investigated.

Therefore, we performed a cross-sectional case–control study in a well-defined group of elderly type 2 DM patients living independently at home to describe the neuropsychological profile in detail. Secondly, we investigated the relationships between cognitive performance and magnetic resonance imaging (MRI) measures as well as DM related determinants (e.g. glycosylated haemoglobin (HbA_{1c}), DM duration, insulin treatment, hypertension, hypercholesterolaemia and diabetic polyneuropathy).

Patients and methods

The study population consisted of 92 patients with type 2 DM recruited from the department of internal medicine in the St Lucas Andreas hospital during a time period from 2001 to 2004 and 44 control subjects. For inclusion, all patients and control subjects had to be 60 years or older and diabetic patients had to have a diabetic duration of at least 1 year. Patients were recruited irrespective of the presence of cognitive complaints. Control subjects were age-matched healthy spouses or neurological outpatients, visiting the hospital for low back pain or a peripheral nerve problem. Control subjects were without a history of cardiovascular or metabolic disorder. All were recruited by the same neurologist (BvH). Exclusion criteria for patients as well as control subjects were a psychiatric or neurologic disorder (unrelated to type 2 DM) that could influence cognitive function, cerebrovascular accidents, a history of alcohol or substance abuse and dementia. Control subjects were excluded if they had a blood glucose of $\geq$7.0 mmol/l. All participants were functioning independently at home and had good comprehension of the Dutch language. The study was approved by the local Medical Ethical Committee. All subjects gave informed consent.

Information on current health status, medical history, drug prescriptions, smoking behaviour and level of education was obtained by means of interview. Information on the presence or absence of hypertension in the diabetic population was obtained by studying the medical records. Educational attainment was rated on an ordinal scale ranging from 1 (incomplete primary school) to 7 (university degree). Total serum cholesterol/high-density lipoprotein (HDL) ratio, glucose and HbA_{1c} were determined. Blood pressure was measured in upright sitting position using an aneroid sphygmomanometer, which was calibrated regularly. Measurements were done on two different occasions with a minimal interval of 4 weeks. The diagnosis of hypertension in all patients and control subjects was based either on history and the use of antihypertensive medication or if the mean of at least two measurements was systolic $\geq$160 mmHg or diastolic $\geq$95 mmHg [17, 18]. A diagnosis of polyneuropathy was based on history and physical exam.

Cognitive assessment

A subjective memory questionnaire consisting of 24 questions based on the Memory Assessment Clinic (MAC) rating scales was used to obtain information on subjective cognitive function [19, 20]. All information was collected without the help of a proxy.

Objective cognitive assessment included global cognitive screening tests and an extensive neuropsychological test battery. Global cognitive functioning was assessed using the Hiv Dementia Scale (HDS) [21], the Cognitive part of the Cambridge Examination for Mental Disorders of the Elderly [22], which incorporates the Cambridge Cognitive Examination (CAMCOG) and the Mini Mental State Examination (MMSE) [23]. In addition, a battery of standardized neuropsychological tests was administered in order to further characterise the nature of cognitive dysfunction. The examiner was blind to the status (diabetic or non-diabetic) of the patients. Tests of executive functioning included Controlled Oral Word Association Test (COWAT), category fluency (animals, jobs) [24], Trail Making Test B [25] and Stroop Colour-Word Test part III, including the errors [26]. The score of Trail Making Test B divided by Trail Making Test A and the subtraction score of Stroop Colour-Word Test parts III and II were used for analysis. Memory was evaluated using Rey Auditory Verbal Learning Test ([RAVLT], immediate and delayed recall) [27] and Rivermead Behavioural Memory Test (RBMT) Logical Memory Test (immediate and delayed recall) [28]. Speed of mental processing was assessed with the Trail Making Test A, Stroop Colour-Word Test parts I and II. Tests of motor functions included Grooved Pegboard ([GP] dominant and non-dominant hand) Test [29] and the binary choice reaction time of the FEPSY [30]. In order to reduce the number of variables, four composite scores were constituted by calculating the mean of the standardised z-scores across the whole study sample in each domain. The scales were first reversed to correspond with each other. A negative score always represented a lower performance. The validity of this test classification was found to be satisfactory (Cronbach's alpha >0.6 for each cognitive domain).

Brain imaging

Brain MRIs were obtained with a 1.5 T scan (1.5 T, General Electric, Milwaukee, USA). Whole brain axial and coronal fluid attenuated inversion recovery (FLAIR) and axial T2-weighted images were acquired to allow detailed visualization of WML and lacunar infarcts. Coronal FLAIR images and sagittal T1-weighted images were acquired to allow measurement of medial temporal lobe atrophy (MTA) and cerebral atrophy. The MRI scans were analysed by an experienced rater (PhS) who was blinded to all clinical information. The Scheltens' scale was used to assess periventricular hyperintensities (PVH), white matter hyperintensities (WMH), basal ganglia hyperintensities (BGH) and infratentorial foci of hyperintensities [31]. Total scores and subscores were used for analysis, whereby a total of deep WML (DWML) was derived by summing WMH and BGH scores.

Cerebral atrophy and MTA were measured by a five point visual rating scale [32, 33]. Mean scores of left and right MTA were used for analysis. Lacunar infarcts were defined as focal hyperintensities corresponding to cerebrospinal fluid on FLAIR and T2 sequences (<5 mm). The number of patients with lacunar infarcts ($n \geq 1$) was used for analysis.

Table 1. Characteristics of the study population

	Type 2 DM	Control subjects
Number	92	44
Age (years (s.d.))	73.2 (5.7)	72.9 (5.3)
Sex m/v	40/52	20/24
Duration of DM(years (s.d.))	13.8 (10.8)	—
Education (median)	4.0 (1.6)	4.5 (1.5)
Current smokers (yes/no)	9/83	6/38
Hypertension (N)	49*	4
Systolic BP mmHg	147 (18)	143 (15)
Diastolic BP mmHg	79 (9)*	83 (8)
Cholesterol/HDL	4.4 (1.4)	4.6 (1.4)
HbA_{1c}	7.7 (1.0)*	5.7 (1.1)
DM treatment:		—
OAD (N)	24	
Insulin (N)	66	
Diet (N)	1	

DM, Diabetes Mellitus; OAD, oral anti-diabetics; BP, blood pressure; HDL, high density lipoprotein.
Data are expressed as means (SD) unless otherwise mentioned, analyses were done with ANOVA, Chi square tests or Kruskal–Wallis tests when appropriate;
*signifies $P<0.05$ compared to the control group.

Statistical analysis

Data were analysed with SPSS for Windows statistical package (release 12.0, SPSS, Chicago, IL). Baseline differences between groups were assessed using independent sample *t*-tests, Mann–Whitney U tests and $[Chi]^2$ tests as appropriate. Neuropsychological test performance was studied using analysis of variance (ANOVA) with sex, age, education and hypertension as covariates. Magnitude of effect size (Cohen's d) for each cognitive domain and individual neuropsychological test was calculated as the mean group difference divided by the pooled standard deviation [34]; a negligible effect is defined if $d \leq 0.2$, a small effect if $0.2<d \leq 0.5$, a medium effect if $0.5<d \leq 0.8$ and a large effect if $d>0.8$.

Multiple linear regression analyses were performed to examine independent associations between MRI measures and cognitive impairment in the diabetic population. The different cognitive domains were used as the dependent variables and the MRI measures were the independent variables. In addition, age, sex, education and hypertension were entered as covariates. WML (low/high) and atrophy scores (low/high) were dichotomized at the respective sample medians. Interactions between the different MRI lesions were tested with ANOVA. A second linear regression analysis was performed to investigate relationships between the cognitive domains and DM disease variables. All statistical tests were two-tailed and significance was accepted at a level of $P<0.05$.

Results

The groups were comparable with regard to sociodemographic factors, systolic blood pressure and cholesterol/HDL (Table 1). Diastolic blood pressure was lower in diabetic patients compared to control subjects. Owing to technical problems data for the motor tests were not available in 16 patients. The neuropsychological test results are presented in Table 2. MRI data were inconclusive in two patients due to claustrophobia and eight patients withdrew from the MRI study. No differences were detected in the subjective memory scale between both groups and the composite z score of the memory functions, whereas all global test scores and other composite z scores differed significantly in the diabetes group compared to control patients with small to medium effect sizes. When hypertension was not controlled the patient group also differed significantly in memory functions (results not shown). The results were also analysed by using the raw scores of the neuropsychological tests. ANOVA with age, sex, education and hypertension as covariates revealed lower scores in diabetic patients on all tests with small to medium effect sizes. Significance was reached on verbal fluency (jobs category), letter fluency, delayed recall of RBMT, GP dominant hand and GP non-dominant hand (Table 2).

Multiple linear regression analyses were performed to investigate the independent contribution of PVH, DWML, MTA, global atrophy and lacunar infarcts to impairment in several cognitive domains (Table 3). In addition, age, sex, education and hypertension were entered as covariates in all analyses. Only PVH was independently associated with motor speed ($\beta = -0.269$, $P = 0.04$), whereas all other MRI measures were not associated with cognitive decline. There were no interactions between PVH, DWML, global atrophy, MTA and lacunar infarcts.

In addition, a second linear regression analysis was performed to predict cognitive deterioration in diabetic patients with DM related determinants (e.g. duration of the disease, HbA_{1c}, insulin therapy, hypertension, cholesterol/HDL and

Table 2. Results of the subjective memory questionnaire, global cognitive functioning tests, different cognitive domains and individual neuropsychological tests

	DM	Control subjects	*P*-value	d
MAC	3.28 (0.40)	3.32 (0.48)	0.719	
HDS	10.2 (3.7)	13.0 (3.2)	0.001	0.84
MMSE	27.2 (2.1)	28.3 (1.5)	0.026	0.65
CAMCOG	93.0 (7.5)	98.1 (9.2)	0.008	0.59
Cognitive domains:				
Z executive functioning	−0.106 (0.68)	0.268 (0.60)	0.014	0.37
Z memory	−0.118 (0.82)	0.273 (0.83)	0.092	0.39
Z mental speed	−0.133 (0.88)	0.294 (0.78)	0.035	0.43
Z motor speed	−0.027 (0.77)	0.290 (0.51)	0.001	0.32
Individual tests:				
Executive functions				
Trail Making Test B division score (B time/A time)	2.9 (1.3)	2.5 (0.8)	0.37	0.35
Stroop III, subtraction score (Stroop III time − Stroop II time)	88.3 (48.8)	76.1 (58.1)	0.26	0.23
Stroop III errors	4.1 (7.7)	3.1 (8.7)	0.45	0.13
Verbal fluency, animals	17.6 (5.5)	20.1 (4.8)	0.08	0.48
Verbal fluency jobs	12.2 (4.2)	14.4 (3.2)	0.02	0.57
Letter fluency	24.8 (11.4)	32.1 (11.3)	0.01	0.65
Memory				
Rey Auditory Verbal Learning Test immediate recall	9.6 (2.8)	10.6 (2.9)	0.52	0.36
Rey Auditory Verbal Learning Test delayed recall	7.2 (3.2)	8.6 (3.6)	0.30	0.42
Rivermead Behavioural Memory Test immediate recall	14.9 (6.2)	17.7 (6.0)	0.06	0.46
Rivermead Behavioural Memory Test delayed recall	10.9 (5.9)	13.7 (6.2)	0.03	0.47
Speed of mental processing				
Trail Making Test A, sec	57.1 (22.5)	46.5 (21.2)	0.12	0.48
Stroop I, sec	51.9 (12.1)	47.2 (11.4)	0.05	0.40
Stroop II, sec	65.5 (16.3)	58.7 (12.3)	0.06	0.45
Speed of motor functions				
Grooved Pegboard (dominant hand), sec	105.1 (35.2)	85.1 (22.8)	0.001	0.63
Grooved Pegboard (non-dominant hand), sec	114.3 (41.6)	99.1 (27.3)	0.004	0.41
Binary choice (FEPSY), ms	653.5 (200.3)	601.4 (105.8)	0.12	0.30

MAC, Memory Assessment Clinic rating scale; HDS, HIV dementia scale; MMSE, Mini Mental State Examination; CAMCOG, Cambridge Cognitive Examination; d, effect size estimate; sec, seconds; ms, milliseconds.

Data for the MAC and for the global cognitive functioning tests are expressed as means (s.d.); analyses were done with Mann–Whitney U tests; Data for the different cognitive domains are expressed as mean standardized values or z scores (s.d.), negative values always represent lower performance, data for the different individual neuropsychological tests are expressed as means (s.d.); ANOVA was used for analyses with age, sex, education and hypertension as covariates. Effect sizes were expressed as Cohen's d.

polyneuropathy) as the independent variables. Only the duration of DM was independently associated with the domain motor speed (standardized $\beta = -0.226$; $P = 0.04$) and HbA_{1c} with the HDS score (standardized $\beta = -0.217$; $P = 0.015$), whereas all other variables were not.

Discussion

Despite the fact the patients did not express cognitive complaints we demonstrated that global cognitive test scores and neuropsychological scores were worse for each cognitive domain except for memory functions after adjustment for hypertension in a group of elderly independently living patients with type 2 DM compared to healthy control subjects. The contribution of MRI measures to cognitive impairment, however, was equivocal. Only PVH were independently associated with motor speed, whereas all other MRI measures were not associated with cognitive performance in the diabetic population. Interactions between the different MRI measures were not present. HbA_{1c} and the duration of DM were significantly associated with some cognitive dysfunction, whereas the other DM related determinants were not.

Other studies showed different results with regard to neuropsychological test scores between subjects with type 2 DM and controls [3, 5]. Important reasons could be the use of different cognitive batteries and a different way of analysing the results of these tests. In our study we used two analytical approaches to assess neuropsychological performance of DM patients, including comparison to healthy controls on composite measures of specific cognitive domains and comparison of the magnitude of deficits on individual measures.

Although a critical review published in 1997 [1] reported that the most commonly affected cognitive ability in subjects with type 2 DM was verbal memory, our finding of a non-significant difference in memory functions after adjustment for hypertension is consistent with the results of other studies [3]. Some studies found also non-significant differences

Table 3. Associations between medial temporal lobe atrophy, global atrophy, deep white matter lesions and periventricular hyperintensities and cognitive domains

	Adjusted R^2	β PVH	β DWML	β MTA	β global atrophy	β lacunar infarcts
MMSE	0.828	0	0.105	0.072	−0.058	−0.124
CAMCOG	0.164	0.076	0.204	−0.019	−0.112	−0.107
HDS	0.368	0.036	0.061	0.023	−0.034	0.049
Executive functions	0.268	−0.167	0.117	−0.100	−0.164	0.091
Memory	0.210	−0.037	0.195	−0.069	0.013	−0.004
Mental speed	0.177	−0.185	0.220	0.011	−0.199 ($P = 0.086$)	−0.033
Motor speed	0.335	−0.269[a]	0.238	−0.080	−0.103	0.122

PVH, periventricular hyperintensities; DWML, deep white matter lesions; MTA, medial temporal lobe atrophy; MMSE, Mini Mental State Examination; CAMCOG, Cambridge Cognitive Examination; HDS, HIV dementia scale.

Linear regression analyses with cognitive domains as dependent variables were performed. PVH, DWML, MTA, cerebral atrophy, lacunar infarcts, age, sex, education and hypertension were entered as independent variables. Regression coefficients were standardized to enable direct comparison of their effects on cognitive functions.

[a] $P<0.05$.

and small or negligible effect sizes after controlling for hypertension, but in general their overall cognitive assessment was relatively brief [3, 5].

Recently, Manschot *et al.* reported the results of their study on cognitive testing and MRI correlates in type 2 DM in patients recruited from general practioners [35]. Our results on cognitive performance in a different population were in line with their results. They also found impaired cognitive performance in all cognitive domains in diabetic patients but statistically significant changes only in the domains executive functioning, information processing speed and memory. After adjustment for hypertension their results were not affected, but we showed that after adjustment for hypertension no statistically significant difference was found for the memory domain. Although our study population was older, had a longer DM duration and worse metabolic control, no associations were found between cognitive impairment and MRI abnormalities in the diabetic population except for PVH. This could be due to the fact that they included patients with a history of stroke, which may implicate that their study population had more advanced cerebrovascular disease than our patients. Moreover, Prins *et al.* reported in a prospective study that white matter lesions, brain infarcts and generalized brain atrophy were associated with decline in information processing speed and executive function. After exclusion of participants with an incident stroke some of the associations were no longer significant, which may indicate that stroke plays an intermediate role in the relationship between cerebral small vessel disease and cognitive decline [36].

We only found an independent association of PVH with motor speed. This finding is supported by other studies, which also found an association between cognitive dysfunction and PVH, but not with DWML, although analyses were not performed in DM patients [37, 38]. However, it is important to realize that the definition of PVH differed in the studies [39]. In the present study PVH was defined as hyperintensities adjacent to the ventricles and not exceeding 10 mm.

A non-significant trend towards an association between mental speed with global atrophy was found, while other studies reported associations with white matter disease for this particular cognitive domain [38, 40]. Our results confirm the suggestion that cognitive impairment in elderly subjects with type 2 DM is due to more complex pathology and not just cerebrovascular disease or cerebral atrophy [7].

No significant differences were detected in a subjective memory questionnaire between DM patients and controls. This illustrates that objective testing is important in diabetic patients to detect cognitive dysfunction. Global cognitive screening tests may be sufficient for detecting cognitive dysfunction and the HDS seems to be the most clinically relevant test.

Associations between global cognitive function and HbA_{1c} may suggest that optimal glycaemic control is necessary even in the elderly patients. Furthermore duration of the disease seems to be important in diminished motor speed tasks, whereas our results show that insulin treatment, diabetic polyneuropathy, hypertension and cholesterol/HDL were not independently associated with cognitive performance in type 2 DM patients.

Among the limitations of our study is the lack of data on known vascular complications of DM. It would have been interesting to associate cognitive decline with other long-term complications as retinopathy, nephropathy and peripheral vascular disease, since some studies show a relation of retinopathy with vascular brain lesions and cognitive impairment. One study reported an association between background diabetic retinopathy and small focal white matter hyperintensities in the basal ganglia and significant cognitive disadvantage [41]. Another study showed that retinopathy is independently associated with poor cognitive function, suggesting that cerebral microvascular disease may contribute to the development of cognitive impairment [42]. While we used visual rating scales, more sophisticated MRI analyses, like volumetry, may reveal significant correlations with structural brain changes and cognitive impairment in diabetic patients. Another possible limitation is that our

findings are based on selected outpatients. Therefore we cannot extrapolate our findings to the general population of type 2 DM patients. Finally, the number of diabetic patients is relatively small and these findings need to be replicated in a larger group preferably with a longitudinal design.

In conclusion, the data of this cross-sectional study show that patients with type 2 DM have diminished cognitive function in different cognitive domains, while memory is less affected after adjustment for hypertension. The association of cognitive impairment with MRI measures is equivocal, but may support a dual pathology involving vascular disease as well as cerebral atrophy and probably yet unknown factors. Metabolic control of DM as well as the duration of DM seem to be important disease variables in the impaired cognitive performance. Regular assessment of cognitive function should be performed as part of the routine review of diabetic patients.

Key points

- Patients with type 2 diabetes mellitus have diminished cognitive functioning on different cognitive domains and global cognitive tests, except for memory functions after adjusting for hypertension.
- Only periventricuar hyperintensities were independently associated with the domain motor speed in patients with type 2 diabetes mellitus, while none of the other MRI measures was associated with cognitive impairment.
- HbA_{1c} and duration of diabetes were both significantly associated with cognitive dysfunction in patients with type 2 diabetes mellitus.

Conflicts of interests

Conflict of Interests Statement: None

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