Original Article

Cognitive Performance, Psychological Well-Being, and Brain Magnetic Resonance Imaging in Older Patients With Type 1 Diabetes

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Modest cognitive impairment has been reported in young-adult patients with type 1 diabetes. In older patients with type 2 diabetes, cognitive impairments are more pronounced, which might be due to age but also to differential effects of type 1 diabetes and type 2 diabetes on the brain. This study therefore assessed cognitive performance and magnetic resonance imaging (MRI) of the brain in older type 1 diabetic patients. Forty type 1 diabetic patients (age >50 years) and 40 age-matched control subjects were included. Neuropsychological assessment included all major cognitive domains, and psychological well-being was assessed with questionnaires. Atrophy, white-matter abnormalities, and infarcts were rated on MRI scans. Type 1 diabetic patients performed slightly (effect sizes <0.4) worse on cognitive tasks, but only "speed of information processing" reached statistical significance. No significant between-group differences were found on any of the MRI parameters. Type 1 diabetic patients tended to report more cognitive and depressive problems than control subjects, but this did not correlate with the performance on cognitive tests. We conclude that cognition in older type 1 diabetic patients is only mildly disturbed. Chronic exposure to hyperglycemia is in itself, even at older age, apparently not sufficient to have considerable impact on the brain. *Diabetes* 55:1800–1806, 2006

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BCR, bicaudate ratio; BDI-II, Beck Depression Inventory-II; BFR, bifrontal ratio; CFT, Complex Figure Test; DWML, deep white-matter lesion; MRI, magnetic resonance imaging; PWML, periventricular white-matter lesion; WAIS-III, Wechsler Adult Intelligence Scale, third edition; WML, white-matter lesion.

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Type 1 diabetes is associated with gradually developing end-organ damage in the brain (1). Cognitive performance in adult patients with type 1 diabetes has been the subject of several studies. Although the results of these studies are relatively heterogeneous with respect to the severity and nature of the affected cognitive domains, a recent meta-analysis clearly shows that cognitive function is mildly impaired in patients with type 1 diabetes relative to control subjects, mainly reflected in a slowing of mental speed and a diminished mental flexibility (2). Thus far, all studies addressing cognition in type 1 diabetes examined cognition in children or young adults. In contrast, most studies assessing cognitive functioning in patients with type 2 diabetes have been performed in older patients. Cognitive deficits appear to be more pronounced in individuals with type 2 diabetes who are >60–65 years of age (3). Hence, it could be hypothesized that the effects of type 1 diabetes on cognition might also be more pronounced in older individuals.

Although the severity of these cognitive deficits in patients with type 1 diabetes is relatively modest (i.e., within 0.5 SD of the control group or an equivalent effect size of <0.5), even moderate forms of cognitive impairments can potentially hamper everyday activities, may result in problems in more demanding situations, and as such, might result in elevated feelings of psychological distress. In fact, the relation between psychological well-being and cognition may be bidirectional, because it is well known that emotional disturbances may also be a source of cognitive impairments.

The relation between cognitive impairments and structural changes in the brain is also unclear. Thus far, only a few magnetic resonance imaging (MRI) studies of the brain in type 1 diabetic patients have been published (4–11). Radiological abnormalities involving the subcortical white matter and both cortical and subcortical atrophy have been reported, but unfortunately, the majority of these studies involved small sample sizes and/or lacked appropriate nondiabetic control subjects. The present study therefore aimed to assess the nature and extent of changes in cognition, psychological well-being, and brain MRI in older patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

For inclusion, type 1 diabetic patients had to be 50–80 years of age, functionally independent, and Dutch speaking. Exclusion criteria for all participants were a psychiatric or neurological disorder (unrelated to diabetes) that could influence cognitive functioning, a history of alcohol or substance abuse and dementia, and a fasting blood glucose ≥7.0 mmol/l for control subjects. Subjects with a history of noninvalidating stroke could be included.

For this project and a parallel project on cognition in type 2 diabetes, 40 patients with type 1 diabetes (age 52–77 years), 122 patients with type 2 diabetes (56–80 years), and 61 control subjects (53–78 years) were included between September 2002 and November 2004. Type 1 diabetic patients were recruited through their treating physicians in the three participating hospitals (Zuwe Hofpoort Hospital, Groene Hart Hospital, and University Medical Center, Utrecht, the Netherlands). Fourteen patients had disease onset before or at age 18. From the 26 patients with a disease onset after the age of 18, the diagnosis of type 1 diabetes was based on C-peptide levels <0.1 nmol/l in 14 patients and a disease onset characterized by ketoacidosis in 4 patients (12). From eight patients who were originally diagnosed with type 1 diabetes in other hospitals, these data were not available. In all of these latter patients, the debut of diabetes was characterized by polydipsia, polyuria, and extreme weight loss within a period of months. Control subjects were recruited among the spouses or acquaintances of the type 2 diabetic patients. The study was approved by the medical ethics committee of the University Medical Center Utrecht, and each participant signed an informed consent form.

Education level was recorded using seven categories and transferred to years of education. Premorbid intellectual level was estimated with the Dutch version of the National Adult Reading Test (13). Scores can be translated into estimated IQ scores based on normative data, because performance on this test is considered to reflect "best ever" global cognitive performance and is relatively resistant to the effects of organic brain disease (14).

The present study includes all type 1 diabetic patients (n = 40, age 52–77 years), and 40 control subjects, matched for age with the 40 type 1 diabetic patients (see Table 1 for demographic variables). The groups were well balanced for age but differed with regard to education and estimated IQ (Table 1). Thus, all analyses on cognition, psychological well-being, and brain MRI were adjusted for IQ. All participants performed the neuropsychological assessment. MRI could not be obtained in three patients with type 1 diabetes and in four control subjects because of MRI contraindications, such as claustrophobia or a pacemaker.

Neuropsychological assessment. Neuropsychological tests were chosen to be sensitive to small or moderate differences in ability and to provide an assessment of the major cognitive domains. Trained neuropsychological assessors administered 11 tests in a fixed order, which took ~90 min to complete. In total, 20 test measures were obtained that covered five cognitive domains.

Abstract reasoning was assessed by Raven Advanced Progressive Matrices (12-item short form) (15). Memory was divided into four subdomains. Working memory was assessed by the forward and backward Digit Span of the Wechsler Adult Intelligence Scale, third edition (WAIS-III) (16) and the Corsi Block-Tapping Task (17,18). Immediate memory and learning rate was assessed verbally and nonverbally with the Dutch version of the Rey Auditory Verbal Learning Task (19) and the modified Location Learning Task (20,21). Forgetting rate, as a measure of decay over time, was also calculated with the Rey Auditory Verbal Learning Task and the Location Learning Task. Incidental memory was measured with the delayed recall trial of the Rey-Osterrieth Complex Figure Test (CFT) (22). Information processing speed included the Trail Making Test part A (23), the Stroop Color-Word Test parts I and II (24), and the WAIS-III sub-test Symbol Digit Substitution. Attention and executive functioning consisted of four subdomains. Response inhibition was assessed by the Stroop Color-Word Test Part III (24). Divided attention was assessed with the Trail Making Test part B (23), controlling for baseline performance on Trail Making Test part A. Concept shifting was assessed by the Brixton Spatial Anticipation Test (25). Verbal fluency was assessed both with a category naming task (animal naming; 2 min) and two lexical fluency tasks (N and A; 1 min each) (26). Finally, visuoconstruction was assessed by the copy trial of the CFT (22).

Assessment of psychological well-being. As an index of overall cognitive, psychological, and physical complaints, the Dutch version of the Symptom Checklist (SCL-90-R) (27) was completed by participants. The SCL-90-R obsessive-compulsive subscale can be seen as indicative of subjectively perceived cognitive performance difficulties in patients (28) and is presented as such. To determine the possible influence of depressed mood, the Beck Depression Inventory-II (BDI-II) was administered (29).

MRI protocol. The MRI investigation (0.5 Tesla; Elscint Gyrex, Haifa, Israel) (1 Tesla; Siemens, Munich, Germany) (1.5 Tesla; Philips Medical Systems, Best, the Netherlands) consisted of an axial T1-weighted and an axial T2 and T2 fluid-attenuating inverse recovery scan (TR/TE/TI: 6,000/100/2,000, FOV 230 mm, matrix 180 × 256, slice thickness 4.0 mm, and contiguous slices 38). There were no systematic differences between the different MRI scanners with regard to the MRI outcome measures. White-matter lesions (WMLs), number and location of infarcts, and cortical atrophy were rated on hard copies or on digital images on a personal computer.

WMLs were distinguished into periventricular and deep (subcortical) regions and rated according to the Scheltens rating scale (30). Periventricular WMLs (PWMLs) were rated on a severity scale (0–2) at the frontal and occipital horns and the body of the lateral ventricle, at the left and at the right side, with the total PWML score being the sum of these six scores (range 0–12). This is a slight modification of the Scheltens scale, because we summed left and right scores, whereas in the original scale, only the side with the highest score is counted (range 0–6).

For the rating of deep WMLs (DWMLs), the brain was divided into six regions: frontal, parietal, occipital, temporal, basal ganglia, and infratentorial. This is an additional minor modification of the Scheltens rating scale (30) that subdivides the basal ganglia and infratentorial regions into five and four different smaller subregions, respectively. Per region, the size and number of the WMLs were rated on a scale ranging from 0 to 6, with the total DWML score being the sum of these six scores (range 0–36).

Furthermore, brain infarcts were scored by location (cortical and subcortical), size (lacunar or large), and number. A lesion was considered a lacunar infarct if its appearance was hypo-intense on T1 and fluid-attenuating inverse recovery images and if its appearance was unlike a perivascular space.

TABLE 1
Demographic and general medical characteristics of patients and control subjects

Characteristic	Control subjects	Type 1 diabetic patients
n (male/female)	40 (16/24)	40 (23/17)
Mean age (years)*	61.6 ± 5	60.9 ± 6†
Education level (median)‡	4 (4–5)	5 (4–6)§
Estimated IQ	101.2 ± 14.1	108.1 ± 11.7§
BMI (kg/m^2)	27.3 ± 5.1	23.7 ± 2.3‖
Systolic blood pressure (mmHg)	135.2 ± 18.8	142.0 ± 22.6
Diastolic blood pressure (mmHg)	79.7 ± 11.1	73.5 ± 9.9§
Hypertension (%)*¶	38	45†
Atherosclerotic disease (%)*#	20	25†**
Fasting triglycerides (mmol/l)	1.7 ± 1.2	0.9 ± 0.5‖
Fasting serum cholesterol (mmol/l)	5.9 ± 1.1	5.3 ± 0.9§
Hypercholesterolemia (%)*††	48	35†
A1C (%)*	5.5 ± 0.4	7.7 ± 1.0†‖
Retrograde A1C (%)*‡‡	—	7.7 ± 0.9†

Data are given as means ± SD or median (interquartile range) unless otherwise indicated. §$P < 0.05$; ‖$P < 0.001$. *Entered as explanatory variable in exploratory regression analyses with cognition or MRI as dependent variables within the type 1 diabetic group; statistically significant association with any cognitive domain scores are indicated as **$P < 0.05$; statistically significant association with any MRI outcome measure are indicated as **$P < 0.05$. Details are provided in RESULTS. ‡Education level was recorded using seven categories that can be transferred to years of education: <6, 6–7, 8–9, 10–11, 12–18, and >18, respectively. ¶Hypertension is defined as an average systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg and/or self-reported use of blood pressure–lowering drugs. #Atherosclerotic disease is defined as suffering from self-reported angina pectoris, myocardial infarction, stroke, or intermittent claudication. ††Hypercholesterolemia is defined as a fasting cholesterol >6.2 mmol/l and/or self-reported use of cholesterol lowering drugs. ‡‡Retrograde data (up to 5 years, mean 3.9 years, mean intra-individual variation coefficient 4.1%) on A1C levels were obtained through the case records.

Cortical atrophy was evaluated quantitatively by the frontal interhemispheric fissure ratio: the maximal width of the interhemispheric fissure from any of the cuts demonstrating the frontal horns of the ventricles, divided by the trans-pineal coronal inner table diameter (31); and by the Sylvian fissure ratio: the average of the maximal Sylvian fissure widths taken from the cut showing the widest Sylvian fissure, divided by the trans-pineal coronal inner table diameter (31). Subcortical atrophy was evaluated by the bicaudate ratio (BCR) measured on the cut best showing the caudate nuclei and by the bifrontal ratio (BFR) measured on the same cut as the BCR. BCR and BFR are defined as the minimal distance between the caudate indentations of the frontal horn (31) or the distance between the tips of the frontal horns divided by the distance between the inner tables of the skull along the same line (31), respectively.

These scales for rating atrophy and WMLs have been validated previously and have a fair to good intra- and interrater reliability (e.g., refs. 32 and 33). For example, the Pearson correlation coefficients for two raters were 0.87 for the DWML score and 0.62–0.90 for the atrophy ratios. Nevertheless, in case of disagreement of more than one point on the WML scale and the template atrophy scale or >2 mm on the atrophy ratios, a consensus reading was held. In all other cases, the readings of both readers were averaged.

Recording of medical history and biomedical measures. Standard medical care for all type 1 diabetic patients in this study included a 3-monthly visit to the clinic for evaluation of the general condition (HbA_{1c} [A1C], fasting triglycerides, cholesterol, and blood pressure) and a yearly monitoring of microvascular complications, including examination by an ophthalmologist and neuropathy assessment by the treating physician (questioning about symptoms, sensory examination, and ankle reflexes). For the purpose of this study, data on retinopathy and neuropathy were derived from medical records, and these complications were rated as absent or present. A history of clinically manifest atherosclerotic disease was defined as self-reported angina pectoris, myocardial infarction, stroke, or intermittent claudication as assessed with the Rose questionnaire (34). Previous occurrence of severe hypoglycemic episodes was assessed with a questionnaire and defined as an episode that required external assistance for recovery (35). Episodes that resulted in seizure or loss of consciousness were also recorded. Furthermore, all participants had their blood pressure measured two times during the assessment.

Statistical analysis. Between-group differences were examined across the groups with a general linear model multivariate analysis, regression analysis, and χ^2 test, as appropriate. Because the groups differed significantly in estimated premorbid IQ (control, 101.2 ± 14.1; type 1 diabetes, 108.1 ± 11.7; $P < 0.01$) and educational level (control, 4 [3–5]; type 1 diabetes, 5 [4–6]); $P < 0.05$), the variable "estimated premorbid IQ" was entered as a covariate in the analyses on cognition, psychological well-being, and brain MRI. Sex was also entered as covariate in these latter analyses.

To compare the five different cognitive domains, the raw test scores were standardized into z-scores. Subsequently, domain scores were calculated by averaging the standardized test scores that contributed to the five respective domains as described in NEUROPSYCHOLOGICAL ASSESSMENT. In addition, a cortical atrophy z-score (mean of standardized frontal interhemispheric fissure ratio and Sylvian fissure ratio) and subcortical atrophy z-score (mean of the standardized BCR and BFR) were calculated. These z-scores were used in linear regression analysis to explore the relation between data on brain structure with cognitive functioning in type 1 diabetes.

RESULTS

Table 2 summarizes the characteristics related to diabetes. The patients had diabetes for an extended period of time (average 34 years), but taking into account the average age of over 60, this duration reflects a relative late onset of type 1 diabetes. General biomedical characteristics that may be related to vascular disease or cognitive decline, such as BMI, fasting triglycerides, and the prevalence of hypertension or hypercholesterolemia, in the diabetic group were similar to the control subjects or even better regulated. In contrast, considering biomedical characteristics specific to diabetes, type 1 diabetic patients in this study show more microvascular complications and hypoglycemic episodes compared with previous studies on cognition in younger adults with type 1 diabetes (2).

Neuropsychological domain scores (adjusted z-scores ± SE [95% CI]) of the groups are presented in Table 3. The general linear model multivariate analysis with estimated premorbid IQ as covariate with the five domain scores as dependent variables was overall significantly different [$F(5,71) = 2.8$, $P = 0.023$, $\eta^2 = 0.17$], indicating an overall worse performance in the type 1 diabetic group. The diabetic group performed significantly worse than control subjects on speed of information processing. Also, the multivariate analysis of all 20 raw test scores corrected for estimated IQ showed highly significant differences [$F(19, 50) = 2.7$, $P = 0.003$, $\eta^2 = 0.50$]. Exclusion of the patients in whom the specific criteria on which the clinical diagnosis type 1 diabetes was initially based could not be confirmed with certainty did not affect the results.

Inspection of all 20 adjusted mean test scores revealed that, except for CFT copy trial, WAIS-Digit Span, and Corsi Block-Tapping Task, type 1 diabetic patients performed slightly worse on all measures (data not shown). Because the domain visuoconstruction consists only of the CFT copy trial, this finding is directly reflected in the performance on this domain.

Results on psychological well-being are presented in Table 4. None of the patients and only one control subject scored above the cut-off criterion of 16 on the BDI-II, indicative of clinical depression (36). Overall, type 1 diabetic patients scored higher on all psychological complaints scales, but this reached significance only in the subscales depression, cognitive performance difficulty, and anger-hostility of the SCL-90-R. Depressive symptoms (expressed as BDI-II scores) were not significantly related to cognitive performance.

Only one patient and one control subject were without any DWMLs. All individuals showed at least some degree of PWMLs. WML severity and the prevalence of infarcts did not differ between the groups. All atrophy ratios were

TABLE 2
Diabetic characteristics of type 1 diabetic patients

Characteristic	Type 1 diabetic patients
Duration of diabetes (years)*	34.0 ± 12.8†
Use of insulin pump*	48
Disease onset before age 18 years*	33†‡
Previous severe hypoglycemic event requiring assistance*	75
Hypoglycemic event leading to seizure or unconsciousness*§	65
Retinopathy	58
Retinopathy with laser treatment	65
Neuropathy	45
Diabetic foot	9
Microvascular complications*‖	70

Data are means ± SD or percent. *Entered as explanatory variable in exploratory regression analyses with cognition or MRI as dependent variables within the type 1 diabetic group; statistically significant association with any cognitive domain scores are indicated as †$P <$ 0.05; statistically significant association with any MRI outcome measure are indicated as ‡$P < 0.05$. Details are provided in RESULTS. §In the regression analyses, the group that experienced hypoglycemia with seizure or unconsciousness was compared with the group that never experienced any severe hypoglycemic event. ‖Microvascular complications were entered in the exploratory regression analyses in two ways: as a dichotomous variable defined as the absence or presence of retinopathy or neuropathy or as a sumscore (range 0–3) in which 1 point was given for neuropathy, 1 point for retinopathy without laser treatment, or 2 points for retinopathy with laser treatment. Neither analysis showed significant associations with MRI or cognition.

TABLE 3
Cognitive performance

Cognitive domains and tests	Control subjects	Type 1 diabetic patients	Mean dif (95% CI)
Abstract reasoning	0.09 ± 0.15	−0.09 ± 0.15	−0.18 (−0.62 to 0.25)
Memory	0.09 ± 0.07	−0.08 ± 0.07	−0.17 (−0.36 to 0.02)
Working memory	−0.05 ± 0.11	0.05 ± 0.11	0.10 (−0.22 to 0.42)
Immediate memory and learning	0.11 ± 0.09	−0.09 ± 0.09	−0.21 (−0.48 to 0.06)
Forgetting rate	0.15 ± 0.13	−0.12 ± 0.13	−0.26 (−0.63 to 0.13)
Incidental memory	0.15 ± 0.16	−0.15 ± 0.16	−0.30 (−0.76 to 0.16)
Information processing speed	0.16 ± 0.10	−0.17 ± 0.10	−0.34 (−0.63 to −0.04)*
Attention and executive function	0.07 ± 0.08	−0.07 ± 0.08	−0.13 (−0.37 to 0.10)
Visuoconstruction	−0.28 ± 0.15	0.28 ± 0.15	0.56 (0.13–0.98)*

Domain scores are presented as adjusted z-scores ± SE. Mean dif: the adjusted between group difference (type 1 diabetic patients − control subjects) in the univariate ANOVA; scores are adjusted for estimated premorbid IQ. Negative z-values indicate worse performance. *$P < 0.05$.

slightly but not statistically significantly higher in the type 1 diabetic patients (Table 5). MRI results were not statistically significant related to cognitive functioning either in control subjects or in the diabetic group. Relations within the type 1 diabetic group among cognitive performance, MRI measures, and biomedical characteristics were explored with linear regression analyses. Statistically significant associations between disease variables and cognitive and MRI outcome measures are shown in Tables 1 and 2. Age ($\beta = -0.459$, $P < 0.001$), hypertension ($\beta = -0.490$, $P < 0.001$), A1C ($\beta = -0.283$, $P < 0.05$), and retrograde A1C ($\beta = -0.296$, $P < 0.05$) were inversely related to speed of information processing. Duration of diabetes was inversely related to memory ($\beta = -0.337$, $P < 0.05$) and to attention and executive functioning ($\beta = -0.331$, $P < 0.05$). Disease onset before age 18 was also inversely related with attention and executive functioning ($\beta = -0.393$, $P < 0.05$). Furthermore, disease onset before age 18 ($\beta = 0.356$, $P < 0.05$) and atherosclerotic disease ($\beta = 0.432$, $P < 0.05$) were related to PWMLs.

DISCUSSION

This study is the first to assess cognitive functioning in older patients with type 1 diabetes and to relate this to structural abnormalities in the brain. Although performance on most tasks was within the normal range, indicating that this group of patients did not have marked cognitive impairments or general cognitive deterioration, older type 1 diabetic patients performed overall slightly worse compared with nondiabetic control subjects. In general, the pattern of cognitive dysfunction can be characterized as rather nonspecific, in which cognitive performance is overall slightly decreased. There was a significantly worse performance in speed of information processing, but then again, the patients were significantly better on visuoconstruction. This should not be interpreted as a deficit in visuoconstructional praxis in the control subjects, because the mean score of both groups is well within the normal range. This test is also considered to be highly sensitive to the level of mental effort delivered on cognitive tasks (14), and therefore it could be interpreted as a reflection of motivation of the subjects.

Type 1 diabetic patients subjectively experienced more cognitive problems than control subjects. On the one hand, this could be seen as a reflection of cognitive performance difficulties, but the actual cognitive test performance was unrelated to cognitive complaints. On the other hand, the cognitive performance difficulty scale of the SCL-90-R also consists of elements that reflect obsessive-compulsive behavior, and it has been suggested that type 1 diabetic patients might develop a personality or response style characterized by extreme cautiousness and careful attention to detail, because they are burdened with a disease that requires them to monitor basic biological functions meticulously (37).

Patients did not have significantly higher total scores on the SCL-90-R, which can be regarded as a measurement of global psychological distress (38). Also, considering the rather low BDI scores observed in this study, these results are not in line with the relatively high prevalence of depression in patients with diabetes reported in other studies (39). Patients with clinically significant depressive

TABLE 4
Level of self-reported psychological and physical complaints

Psychological scales	Control subjects	Type 1 diabetic patients	Mean dif (95% CI)
SCL-90-R			
Total Score	116.1 ± 4.04	121.6 ± 4.04	5.59 (−6.10 to 17.27)
Anxiety	12.34 ± 0.44	12.76 ± 0.44	0.42 (−0.86 to 1.69)
Agoraphobia	7.87 ± 0.32	7.93 ± 0.32	0.00 (−0.86 to 0.97)
Depression	20.56 ± 0.84	22.34 ± 0.84	1.79 (−0.63 to 4.20)*
Somatization	18.30 ± 0.84	18.95 ± 0.84	0.65 (−1.77 to 3.07)
Cognitive performance difficulty	12.55 ± 0.58	14.53 ± 0.58	1.98 (0.30–3.65)*
Interpersonal sensitivity and paranoid ideation	21.92 ± 0.88	24.21 ± 0.88	2.28 (−0.27 to 4.84)
Anger-hostility	6.33 ± 0.29	7.49 ± 0.29	1.16 (0.33–1.99)*
Sleep disturbance	5.42 ± 0.45	6.04 ± 0.45	0.63 (−0.69 to 1.94)
BDI-II	3.96 ± 0.72	5.73 ± 0.71	1.76 (−0.32 to 3.85)

Data are adjusted means ± SE. Mean dif: the adjusted between group differences (type 1 diabetic patients − control subjects) in the univariate ANOVA. All scores are adjusted for estimated premorbid IQ and sex. Higher scores reflect more reported complaints. *$P < 0.05$.

TABLE 5
MRI results in diabetic patients and control subjects

MRI ratings	Control subjects (n = 36)	Type 1 diabetic patients (n = 37)	Mean dif (95% CI)
PWML	6.0 (5.0–6.0)	6.0 (6.0–7.0)	0.5 (−0.5 to 1.0)
DWML	4.0 (2.5–6.0)	3.0 (1.5–6.0)	−1.0 (−3.0 to 1.5)
Cortical atrophy			
FFR (*10)	0.30 ± 0.10	0.33 ± 0.12	0.01 (−0.04 to 0.06)
SFR (*10)	0.31 ± 0.08	0.33 ± 0.10	0.01 (−0.03 to 0.06)
Subcortical atrophy			
BCR	0.12 ± 0.03	0.14 ± 0.03	0.01 (−0.01 to 0.02)
BFR	0.31 ± 0.05	0.33 ± 0.04	0.01 (−0.01 to 0.03)
			OR (95% CI)
(Silent) infarct	8%	8%	1.01 (0.16–6.23)

Data are given as unadjusted means ± SD or median (interquartile range) unless otherwise indicated. Mean dif: the adjusted between group difference (type 1 diabetic patients − control subjects) in the univariate ANOVA. Mean difference and OR were adjusted for estimated premorbid IQ and sex. FFR, frontal interhemispheric fissure ratio; SFR, Sylvian fissure ratio.

symptoms may not have been interested in participating in our rather demanding study protocol. Unfortunately, we have no detailed data on the nonresponders for this study.

We observed that the amount of brain abnormalities based on MRI was within the normal range in both groups. Similar rates of (silent) infarcts and WML severity have been reported in random samples from the general population of the same age-group (40–42). Earlier studies of brain MRI in type 1 diabetes involved younger patients (average age 25–40 years) with an earlier disease onset (average age at onset 10–18 years) (4–9,11). Five previous studies compared measures of cerebral atrophy (7,8,11) or WML severity (4,9) in type 1 diabetic patients (sample sizes <25 in all but one study [11]) with control subjects. One study reported a 25% increase in the BFR (7), and another a 3% decrease in total cerebral volume (8). The most detailed study on cerebral atrophy thus far reported modest regional reductions in cortical gray matter density, using voxel based morphometry (11). A study on WMLs that involved 25 type 1 diabetic patients that all had advanced microvascular complications did not observe WMLs in any of these patients (9). Others reported WMLs in 11 of a group of 16 type 1 diabetic patients and in 5 of 40 control subjects (4). However, if the data from this latter study were translated to the Scheltens DWML scale (30), the median score would be 1, which corresponds with a very small lesion volume (median total DWML volume <0.1 ml), which is compatible with the age of the population involved and still well below our ratings (Table 5). Another study, which did not include nondiabetic control subjects, examined determinants of MRI abnormalities within a population of type 1 diabetic patients (5,10). Neither a history of severe hypoglycemia (contrary to an initial report [6]) nor the presence of retinopathy was associated with cerebral atrophy or WMLs, although retinopathy was associated with an increased occurrence of so-called enlarged perivascular spaces. An early diabetes onset (≤7 years) was associated with a higher ventricular volume but not with cortical atrophy or WML severity (10). The combined results of these previous studies and the present study indicate that MRI changes in the brain of patients with type 1 diabetes are relatively subtle and may be more pronounced in patients with an early diabetes onset. Computer-assisted volumetric measurements are probably more likely to detect such subtle changes than the rating methods that were used in the present study. Nevertheless, our data indicate that there are no marked differences between older type 1 diabetic patients and control subjects on brain MRI.

It is commonly assumed that duration of diabetes and the normal aging process interact in their effects on the brain (43,44). Based on studies on older patients suffering from type 2 diabetes, we hypothesized that cognitive deficits in older patients with type 1 diabetes may also be more pronounced than in younger type 1 diabetic patients. However, the severity of the cognitive impairments observed in the present study is modest (effect sizes ranging from 0.2 to 0.4), which is in line with results of studies on younger adult type 1 diabetic patients (2). Hence, this study does not support our hypothesis. Possibly, this may be due to differences in study design and patient selection between the current study and previous research. A strength of our study is that it combines a detailed analysis of cognitive function and brain MRI in older type 1 diabetic patients, thus allowing the assessment of the relation between these parameters. The main difference with previous studies is not only the age of our study population but, despite the long duration of diabetes, also the relatively late diabetes onset (for overview, see ref. 2). Glycemic control, as reflected in A1C levels, was also relatively low in our patients compared with previous studies (2). This may be due to relative intensive medical care of our patients, also expressed in the high proportion of patients on pump therapy. Nevertheless, the proportion of patients with microvascular complications or a history of severe hypoglycemic episodes was higher than in previous studies (2), which is likely to reflect the extended diabetes duration. The relatively late onset of diabetes may be a possible explanation of the relatively modest effects on cognition that we observed. Age at onset in previous studies on cognition or brain MRI in patients with type 1 diabetes was generally below 20 (2). Studies in children with type 1 diabetes indicate that a very early onset of diabetes (<7 years) is associated with poorer cognitive performance (45). If a similar effect of age exists in patients with an onset before the age of 20 relative to an onset thereafter remains to be determined. Other aspects of population selection may also affect our results. By definition, a study of older type 1 diabetic patients includes "survivors," which implies that relative healthy patients were included in this study. Furthermore, individuals who participate in research projects that include a detailed work-up at a hospital tend to be less affected than those who refuse participation. The performance level on

the copy trial of the RCF test suggests that type 1 diabetic patients were very motivated to participate. The level of education in type 1 diabetic patients was also higher than control subjects, but we adjusted for this potential confounder in the analyses of the MRI and cognition data. Finally, although the occurrence of vascular risk factors (e.g., cholesterol, triglycerides, blood pressure, and BMI) in the control subjects was similar to previous large population-based surveys of older subjects in the Netherlands (for example, see ref. 46), several of these risk factors were relatively less common in the type 1 diabetic group (Table 1). This probably reflects more aggressive risk factor management in type 1 diabetic patients. The combined effects of selection bias and the intensified medical care of the patient group could have lead to an underestimation of the effects of diabetes.

The determinants of impaired cognitive performance and brain MRI changes in patients with type 1 diabetes are still not completely clear (2,10). Exploratory regression analyses in the present study showed relations with chronic exposure to hyperglycemia (A1C and diabetes duration), diabetes onset before age 18, and vascular factors (hypertension and atherosclerosis). It should be noted, however, that our study was not primarily designed to examine the relation between vascular and metabolic factors, diabetes complications, and the outcome measures in detail. This would require a larger number of patients, a more standardized and detailed assessment of diabetes complications, and preferably a longitudinal design (see, for example, refs. 10 and 47).

It can be concluded that older patients with type 1 diabetes performed slightly worse on almost all cognitive tasks, but this is not accompanied by obvious changes on brain MRI. Most importantly, the level of cognitive performance of these older type 1 diabetic patients compared with control subjects is similar to the findings in younger adults with type 1 diabetes (2). Chronic exposure to hyperglycemia is in itself, even at older age, apparently not sufficient to have considerable impact on the brain.

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