

Hippocampal volume and cognitive performance in long-standing Type 1 diabetic patients without macrovascular complications

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Abstract

Aims Hippocampal atrophy and memory deficits have been reported in Type 2 diabetes. Whether similar alterations occur in Type 1 diabetes is currently unknown.

Methods In a case-control design, 13 Type 1 diabetic patients with at least 10 years' duration of disease, but free from clinical signs of macrovascular disease, were compared with age- and gender-matched control subjects. Hippocampal volume and measures of global cerebral cerebrospinal fluid (CSF) were determined from magnetic resonance imaging (MRI) scans. Cognitive functions were assessed using four neuropsychological tests. Mood and depression were measured by questionnaires.

Results Hippocampal volume and memory did not differ between Type 1 diabetic patients and control subjects. However, a significantly increased amount of cerebral CSF suggestive of mild cerebral atrophy was observed in the patients. In addition, deficits in psychomotor speed and selective attention were apparent. Eleven of 13 patients had retinopathy and/or nephropathy. Findings were unrelated to cerebrovascular disease, white matter disease or silent strokes.

Conclusions Results from our small study in Type 1 diabetic patients do not support findings from previous studies of Type 2 diabetic patients demonstrating reductions in hippocampal volume and impaired memory. On the contrary, we observed evidence for mild cerebral atrophy and impaired psychomotor speed and selective attention. This is in line with some previous studies in Type 1 diabetes. If replicated in larger studies, our findings would support the idea that the effects on brain function and structure differ between Type 1 and Type 2 diabetes.

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Keywords attention, hippocampus, magnetic resonance imaging, memory, Type 1 diabetes

Abbreviations BMI, body mass index; CSF, cerebrospinal fluid; DCCT, Diabetes Control and Complications Trial; ICV, intracranial vault; IGF-1, insulin-like growth factor-1; HbA_{1c}, glycated haemoglobin; HPLC, high pressure liquid chromatography; MRI, magnetic resonance imaging

Introduction

Clinical evidence suggests that patients with diabetes have impaired cognitive functions but evidence from controlled

studies is not clear. Several previous studies investigated mixed patient groups with Type 1 and Type 2 diabetes. In a survey of 20 studies which included only Type 1 diabetic patients, at least one aspect of cognitive function was impaired in each study, but the effect sizes were relatively small [1]. Suggested potential mechanisms include direct effects of hypo- or hyperglycaemia and hypo- or hyperinsulinaemia, but also indirect effects via cerebrovascular alterations [1]. A review of longitudinal

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studies in patients with Type 2 diabetes mellitus concluded that they are at increased risk of cognitive decline, even though interpretation was somewhat compromised by confounding factors such as age, smoking history, hypertension and cardiovascular disease [2].

The hippocampus is crucial for declarative (explicit) memory in animals as well as humans [3]. It is also a region with high insulin receptor density as well as insulin sensitive glucose transporters [4,5]. Insulin receptors in the brain have been linked to cognitive function and neurodegenerative diseases [4]. Because of its involvement in memory and its high sensitivity to metabolic disturbances, the hippocampus is a region of interest in diabetes [6].

Global cerebral atrophy is present in a variety of disorders, in particular in cerebral macrovascular disease [7]. Studies in Type 2 diabetes or mixed cohorts predominantly of Type 2 diabetes also reported enhanced global cerebral atrophy [8–10]. In Type 1 diabetes, cerebral atrophy has been demonstrated in a few studies only [11,12]. Reduced hippocampal volumes, as determined from structural MRI, have recently been reported in Type 2 diabetes [13], which is in line with an older CT study [10]. Moreover, in old-age non-diabetic subjects, impaired glucose tolerance was associated with smaller hippocampal volumes [14]. To the best of our knowledge, no previous study has measured hippocampal volumes in adults with diabetes Type 1.

Hypertension is an independent predictor of impaired cognitive function [15] and is present in most patients with long-standing diabetes. To minimize the influence of pre-existing macrovascular disease, we intended to study a homogeneous cohort of middle-aged Type 1 diabetic patients with long-standing disease free from clinical evidence of macrovascular disease and hypertension. Unexpectedly, in an outpatient clinic with 800 diabetic patients, we were not able to ascertain a sufficient number of patients free from hypertension. Therefore, we recruited patients with well-controlled hypertension. In order to measure the impact of Type 1 diabetes on hippocampus structure and function, measurements of hippocampal volumes, global cerebral volumes and cognitive functions were undertaken.

Patients and methods

Setting

The study was designed as a case-control study. Outpatients of the Department of Endocrinology, Diabetes and Rheumatology of Düsseldorf University Medical School who met the inclusion criteria were recruited consecutively during 2003. Patients attended the outpatient clinic at least four times per year (mean 4.7 consultations per year, not counting consultations by phone). At each visit, they were routinely asked about the number of hypoglycaemic events and level of hypoglycaemia awareness. The number or frequency of hypoglycaemia events was noted in the records. When hypoglycaemic events had occurred, we determined whether they had been mild or severe and, if severe, whether treated with intravenous glucose infusion or glucagon

injection. The patients' blood glucose protocol and the blood pressure protocol were looked at and discussed at every visit.

Blood samples for HbA_{1c} were drawn in the outpatient clinic. Neuropsychological tests were performed in a quiet testing room at 18.00 h by a researcher from the Department of Psychology. MRIs were performed in the radiology department located in the same building.

Study population

For the study group, patients with Type 1 diabetes mellitus as defined by WHO criteria were recruited. Students and employees of comparable educational background were recruited as age- and sex-matched control subjects.

Inclusion criteria

Patients 30–50 years of age were included if Type 1 diabetes was present for at least 10 years. Patients with and without microvascular complications were included. Patients without hypertension or with well-controlled hypertension were included if blood pressure was below 140/90 mmHg in the clinic. All patients with hypertension had participated in a structured teaching programme for hypertensive patients designed and evaluated by Sawicki [16]. Patients were trained to measure their home blood pressures and brought their blood pressure documentation every 3 months to the outpatient clinic. All aimed to have home blood pressure values below 135/75 mmHg.

Exclusion criteria

Any history or clinical finding of macrovascular complication such as coronary artery disease, peripheral artery disease, cerebral infarction or ischaemia, history of foot ulcers. Data were obtained from the patient records and clinical investigation including ECG. Macrovascular disease was excluded by standard clinical procedures; angiography was not indicated for any patient.

Further exclusion criteria were metal implantation, previous or current psychiatric disorders (e.g. depression) diagnosed according to ICD 10, excessive alcohol consumption, use of medications that interact with GABA receptors and antihistaminic drugs, history of uncontrolled blood pressure > 200/95 mmHg for more than 6 months, office blood pressures > 140/90 mmHg, therapy with glucocorticosteroids, infectious diseases, severe hypoglycaemia during the week prior to the investigations and also blood glucose levels below 5 mmol/l at the time of the tests.

Definition of hypoglycaemia

Mild hypoglycaemia was defined as blood glucose levels below 3 mmol/l with or without symptoms or below 3.5 mmol/l with symptoms of hypoglycaemia. Severe hypoglycaemia was defined as requiring help from a third party by either intravenous glucose infusion or glucagon injection.

Laboratory methods

HbA_{1c} was measured by HPLC. Glucose was measured photometrically by commercially available devices to ensure that

blood glucose levels were not below 5.0 mmol/l during the tests.

Magnetic resonance imaging data acquisition

Subjects were scanned with a 1 Tesla Philips Gyroscan. After an initial scout image a 3-D T 1 weighted (TR 28 ms, TE 6.9 ms) sagittal image was obtained (200 slices, slice thickness 0.8 mm; FOV 240 mm, matrix 256*256, flip angle 30°). This image was used for volumetric analysis. Then an axial FLAIR Image (TR 5000 ms, TE 100 ms) was obtained (20 slices, slice thickness 5 mm, gap 1 mm, FOV 230 mm, 386*512 matrix, flip angle 90°). This image was clinically assessed by a neuroradiologist (OK) to exclude potential white matter diseases or 'silent strokes'. In one patient initially recruited for the study, a 'silent stroke' was detected. This patient and her matched control were excluded from the study.

Volumetric analysis of the MRI data

Analysis was performed using MIDAS software (Multimodal Image Data Analysis System, WH Tsui, New York University, unpublished). The sagittal scans were used to create coronal images reformatted orthogonal to the plane through the most inferior portion of the frontal and occipital lobes on the mid-sagittal plane. These 1.5-mm-thick coronal images were used for the hippocampus measurements. All measurements were done blind to the clinical diagnosis. Reliable and validated protocols were applied [17,18] by a person (OTW) trained by Professor Convit in those methods. The hippocampus (cornu ammonis, dentate gyrus, and subiculum) was manually outlined in its entire anterior–posterior extension. In order to separate the hippocampus from the adjacent amygdala, multiple image orientations were used [17].

To correct for head size variations, cerebral vault volume was obtained by measuring the volume of the compartment bounded by the dura and the tentorium cerebri on every tenth slice. A measure of global CSF was determined using a threshold procedure to segment the CSF within the cerebral vault volume [17]. The threshold was defined as 50% of the white matter intensity sampled in a standardized fashion. In addition, a measure of cerebral volume was created by subtracting global CSF from the intracranial vault volume. For hippocampal volumes, the right and left hemisphere values of each subject were averaged. In addition, hippocampal, global CSF and cerebral volumes were adjusted for differences in cerebral vault using an analysis of covariance with cerebral vault as covariate.

In order to establish the reproducibility of the volumetric method, nine randomly selected scans were measured again after several months. The coefficient of variation was low for all measures (below 5%) and reliability was high (intraclass correlation coefficient of 0.92 and higher).

Questionnaires

Depression

The German short version of the Center for Epidemiological Studies Depression Scale was used [19]. It contains 15 items and subjects have to rate the presence of specific depressive

symptoms during the last week. The scale for each item ranges from 0 (rarely) to 3 (most of the time).

Mood

An adjective checklist [20] was used to assess the current mood of the subjects. The questionnaire contains three scales, namely: elevated vs. depressed mood, wakefulness vs. sleepiness, and calmness vs. restlessness. Each of the three scales contains eight items. The scale ranges from 1 (not at all) to 5 (very much).

Neuropsychological tests

Four neuropsychological tests were employed based on previous reported impairments in Type 1 (mostly attention and psychomotor speed; see Brands *et al.* [1] and Type 2 diabetes (mostly memory deficits; see Allen *et al.* [2]).

Paired associates (verbal declarative memory)

Seven word pairs of unrelated words were read to the subject. Immediate (three trials) as well as delayed recall (1 trial), about 30 min later, were tested by reading the first word of each pair as a cue. Subjects received 1 point for each correct pair [21].

Stroop Color–Word Interference Test

The task includes three conditions, in which reading time was recorded. The first condition (word reading) required the subject to read 36 colour words (red, green, blue, yellow), presented in rows on a card. The second condition (colour naming) required the naming of colours. The third condition (colour–word interference), consisted of colour names that were printed in discordant colours. The subject had to name the colour of the ink, and was thus required to inhibit the impulse of reading the words themselves. The difference between card 3 and card 2 was used as the interference score [21].

Digit span (verbal short-term memory)

Forwards: series of digits with increasing length were read to the subjects, which they had to repeat. One point was given for each correct sequence.

Backwards: this time the subject had to repeat each sequence backwards [21].

Modified trail-making A (psychomotor speed)

A German version of the trail-making test A was used. This modified version contains 90 instead of 25 numbers. In this test, subjects have to connect encircled numbers on a piece of paper presented in a pseudo random fashion as quickly as possible [22].

Statistical evaluation

Student's *t*-tests were used to compare the two groups. Results of $P < 0.05$ were considered significant while values of $P < 0.10$ were considered to represent a trend. In addition, MRI results were analysed with an analysis of covariance (ANCOVA) in order to control for the influence of intracranial vault on the obtained hippocampal, CSF and cerebral volume measures. Similarly, ANCOVA was used in order to control for a possible influence of wakefulness (measured with a questionnaire; see above) on cognitive test performance. Finally, possible associations

Table 1 Demographic and endocrine characteristics of the patient and control groups; mean \pm SE (range)

	Diabetes mellitus <i>n</i> = 13†	Controls <i>n</i> = 13	<i>t</i> -value	<i>P</i> -level
Age (years)	41.3 \pm 1.3 (35–48)	38.5 \pm 1.5 (31–48)	1.39	0.18
BMI (kg/m ²)	25.1 \pm 1.2 (17.7–34.2)	22.4 \pm 0.8 (19.1–28.0)	1.81	0.08
Formal education (years)	14.5 \pm 0.7 (11.0–18.0)	15.7 \pm 0.6 (11.0–18.0)	–1.32	0.20
Income (Euro)	1500.0 \pm 160.1 (500–2000)	1181.8 \pm 272.0 (500–3000)	1.05	0.31
HbA _{1c} *	8.2 \pm 0.3 (6.6–10.4)	5.3 \pm 0.1 (4.8–6.0)	8.88	< 0.001

*Significant ($P < 0.05$) differences.

†Each group consisted of four female and nine male subjects.

between cognition, HbA_{1c} and the brain measures were investigated for each group separately using partial correlations controlling for intracranial vault.

Ethical considerations

The protocol was approved by the ethics committee of the University of Duesseldorf and all participants provided written informed consent.

Results

Study population

Thirteen subjects could be recruited (nine men and four women). Duration of diabetes was mean 27.7 years, range 14–36 years. Three patients were free from hypertension, 10 patients had arterial hypertension for a mean of 12 years, range 6–19 years. Patients with hypertension had been followed up in our centre for a mean of 12.5 years; the three patients without hypertension have been followed up for a mean of 7.6 years. With the exception of one patient, all patients had been treated for hypertension since diagnosed in our outpatient clinic. The blood pressure was well controlled during follow-up in the outpatient clinic by an average of three anti-hypertensive medications and lifestyle changes. Microvascular complications were present in 11 patients. Ten patients had stable diabetic retinopathy, five had mild peripheral polyneuropathy, nine had diabetic nephropathy and, of these, four patients had stable renal insufficiency. Only two patients were free from any microvascular complication, and one of them was also free from hypertension after 14 years of disease duration. All patients were first seen in our outpatient clinic between 1988 and 1996. As expected, HbA_{1c} was elevated in diabetic patients at 8.2%, corresponding to 24-h average blood glucose values of 10.7 mmol/l.

All patients had experienced mild hypoglycaemia with the exception of one. The one patient was on continuous subcutaneous insulin infusion therapy with high HbA_{1c} around 9.0% for years. Three out of 13 patients had recurrent mild hypoglycaemia at a frequency of more than two times per week. Two

of these also had severe hypoglycaemia in 2002 and 2003 treated with glucagon injection. One of those two patients with a current HbA_{1c} of 6.9% had three episodes of severe hypoglycaemia in 2002 and one in 2003. The other patient, with a current HbA_{1c} of 10.4% had two episodes of severe hypoglycaemia in 2002 and one in 2003. A third patient had a history of two severe episodes of hypoglycaemia in 1988. In no case was professional help or hospital admission necessary.

Control group

Thirteen healthy subjects were recruited. To confirm the absence of arterial hypertension, office blood pressure was measured and ranged from 106/68 to 136/84 mmHg, average 124/78 mmHg. To confirm the absence of diabetes, HbA_{1c} was measured (see Table 1).

Demographic characteristics as well as HbA_{1c} are presented in Table 1. The two groups did not differ in age, years of formal education, and personal income, while a trend ($P < 0.10$) was observed for the diabetic patients to have a higher BMI. Blood glucose levels before cognitive testing were not below 6.2 mmol/l in the diabetic patients.

Mood and depression

Results are presented in Table 2. Diabetic patients did not report more depressive symptoms ($P > 0.10$). They did, however, report significantly less wakefulness ($P < 0.05$) and tended ($P < 0.10$) to report less calmness. No difference was apparent in mood ($P > 0.10$).

Cognitive tests

Results are also presented in Table 2. Diabetic patients tended to be slower in the trail-making test ($P < 0.10$) and showed significantly more interference in the Stroop test ($P < 0.05$).

Because the two groups differed significantly in self-reported wakefulness (see above), we performed an additional analysis in order to exclude the possibility that the cognitive

	Diabetes mellitus <i>n</i> = 13	Controls <i>n</i> = 13	<i>t</i> -value	<i>P</i> -level
Depression	10.2 ± 1.9 (1–20)	6.5 ± 1.3 (1–15)	1.66	0.11
Mood	15.4 ± 0.9 (10–20)	16.2 ± 0.6 (13–19)	–0.72	0.48
Wakefulness*	12.2 ± 0.9 (7–19)	15.2 ± 0.9 (8–20)	–2.40	0.03
Calmness	14.0 ± 0.8 (7–17)	16.2 ± 0.9 (12–20)	–1.80	0.09
Verbal paired associates immediate	11.0 ± 1.1 (5–18)	12.7 ± 0.9 (8–20)	–1.22	0.23
Verbal paired associates delayed	5.0 ± 0.4 (3–7)	5.1 ± 0.4 (3–7)	–0.14	0.89
Modified trail making A (time in s)	93.3 ± 8.7 (61–174)	73.5 ± 4.1 (53–96)	2.05	0.05
Digit span forwards	7.3 ± 0.6 (3–10)	7.5 ± 0.6 (5–12)	–0.27	0.79
Digit span backwards	6.5 ± 0.5 (4–10)	7.5 ± 0.5 (5–12)	–1.33	0.20
Stroop Interference Score*	15.0 ± 1.5 (7–24)	10.3 ± 1.1 (4–16)	2.53	0.02

*Significant ($P < 0.05$) effects.

Table 2 Results of the questionnaires and cognitive tests; mean ± SE (range)

Table 3 Results of the volumetric MRI measurements; mean ± SE (range)

	Diabetes mellitus <i>n</i> = 13	Controls <i>n</i> = 13	<i>t</i> - or <i>F</i> -value	<i>P</i> -level
Intracranial vault (ICV; cm ³)	1218.4 ± 29.6 (1016.6–1415.8)	1282.2 ± 29.6 (1107.5–1493.5)	<i>t</i> = –1.52	0.14
CSF (cm ³)	122.7 ± 11.1 (84.2–222.1)	97.3 ± 5.5 (68.9–127.8)	<i>t</i> = 2.05	0.05
Cerebral volume (cm ³)*	1095.71 ± 26.2 (925.9–1256.8)	1184.86 ± 25.2 (1038.6–1370.8)	<i>t</i> = –2.45	0.02
Hippocampus (cm ³) (average of right and left side)	2.57 ± 0.1 (2.08–2.87)	2.65 ± 0.1 (2.18–2.88)	<i>t</i> = –0.95	0.35
CSF adjusted for ICV (cm ³)*	128.02 ± 7.6	92.01 ± 7.6	<i>F</i> = 10.86	< 0.001
Cerebral volumes adjusted for ICV (cm ³)*	1122.28 ± 7.6	1158.29 ± 7.6	<i>F</i> = 10.86	< 0.001
Hippocampus adjusted for ICV (cm ³)	2.59 ± 0.06	2.63 ± 0.06	<i>F</i> = 0.17	0.69

t-values are from *t*-test for independent samples.

F-values are from ANCOVAs with intracranial vault as covariate.

*Significant ($P < 0.005$) effects.

findings were secondary to differences in wakefulness. We used an analysis of covariance (ANCOVA) with wakefulness as covariate. The inclusion of the covariate did not change the findings. Differences in trail making remained borderline ($P < 0.10$), while differences in the Stroop test remained significant ($P < 0.05$). No differences were observed in the paired associates (verbal declarative memory) or in digit span (short-term/working memory).

MRI findings

Results are depicted in Table 3. Diabetic subjects tended to have a larger amount of global CSF ($P < 0.10$) and had a significantly smaller cerebral volume ($P < 0.05$). When adjusted for intracranial

vault in an ANCOVA, both measures were significantly different between patients and control subjects ($P < 0.01$). This indicates mild cerebral atrophy in the patients. In contrast, hippocampal volumes (unadjusted and adjusted) did not differ between patients and control subjects. All MRI derived volumetric values were within the range of previous studies using this method.

None of the study participants had any signs of clinically relevant white matter disease and/or ‘silent strokes’ as confirmed by analysis of the FLAIR image.

Correlational analysis

Partial correlations (controlling for intracranial vault) revealed that within the patient group ($n = 13$) the amount of cerebral

CSF was significantly associated with poorer performance in the Stroop test ($r = 0.76$; $P < 0.01$) and in the trail-making test ($r = 0.77$; $P < 0.01$). After removal of one outlier, these correlations were no longer significant (CSF and Stroop tests; $r = 0.55$; $P = 0.08$; CSF and trail making; $r = 0.29$; $P = 0.39$). No associations with hippocampal volumes or with HbA_{1c} values were detected. On a descriptive level, the three patients with a history of severe hypoglycaemic episodes did not differ in any of the MRI measures or the cognitive measures from the rest of the patient group. No significant associations between brain measures and cognition were detected in the control group.

Discussion

Volumetric analysis of the structural MRI scans revealed a larger amount of CSF associated with smaller cerebral volumes in the patient group, while no differences were observed for hippocampal volumes. To the best of our knowledge, this is one of the first studies to measure hippocampal volumes in adult patients with Type 1 diabetes. The non-significant findings of the present study are limited by the relatively small sample size and its associated lack of statistical power, and therefore await replication. Absence of hippocampal atrophy has also been described recently in a preliminary report in children with Type 1 diabetes (published in abstract [23]). A second preliminary report in adults with Type 1 diabetes observed a decrease in grey matter density in frontal as well as temporal regions (published in abstract [24]). The latter study suggests that future studies in patients with diabetes should investigate additional regions outside the hippocampus.

The neuropsychological findings of our study are in line with the morphological observations. Patients with Type 1 diabetes showed deficits in psychomotor speed (trail-making test) and selective attention (Stroop), while not showing any evidence for memory deficits (paired associates). The differences in psychomotor speed and selective attention were not secondary to differences in wakefulness as shown using analysis of covariance. The current neuropsychological findings are in agreement with previous results from other groups [1]. For example, young Type 1 diabetic patients demonstrated reduced psychomotor speed, but no difference in memory [25]. Our small study used only four neuropsychological tests; a more detailed neuropsychological evaluation would be desirable in future studies.

Multiple mechanisms have been proposed which could explain the mild cerebral atrophy observed in the patients. In 1965, Reske-Nielsen described the concept of 'diabetic encephalopathy' as a complication of long-term diabetes mellitus [26]. Principally, deviations from normoglycaemia, macrovascular and microvascular disease, and hormonal and cytokine changes are possible mechanisms for cerebral atrophy.

Hyperglycaemia is the most common pathophysiological finding in diabetes. The Diabetes Control and Complications Trial (DCCT) study [27] and further studies have given evidence

that elevated blood glucose levels are associated with higher rates of microangiopathy and consequently possible cognitive impairment, although the opposite has also been found [28]. Tight metabolic control is often achieved at the expense of hypoglycaemic episodes. After mild hypoglycaemia, cognitive function is temporarily impaired [29].

There is also evidence that hypoglycaemic episodes are associated with cerebral atrophy or white matter lesions in Type 1 diabetic patients [1]. In the MRI study by Perros, cerebral atrophy was only observed in patients with a history of hypoglycaemia [30]. Repeated hypoglycaemic episodes have also been associated with persistent cognitive impairment [31–33]. In our cohort, all but a single patient had experienced mild hypoglycaemia. Three patients had reported severe hypoglycaemia. This prevalence is not very different from the results of the DCCT study [34].

Severe hypoglycaemia may trigger the release of excitatory amino acids such as glutamate and aspartate, which trigger calcium influx, activation of proteases and structural cerebral damage. In addition, counter-regulatory hormones may be elevated for hours after a hypoglycaemic episode. In our study, severe hypoglycaemia appeared not to be associated with especially pronounced findings in the MRI scan or in the neuropsychological tests. However, the study sample was too small to conduct a formal statistical evaluation.

Large vessel disease was excluded clinically in our patients, without invasive methods such as angiography because these were not indicated by standard clinical protocols. Screening for clinically silent macrovascular lesions was not performed. Therefore, proof of complete absence of macroangiopathy including aortic plaques or asymptomatic coronary lesions is missing. Hypertension was well controlled in our cohort of patients, but an influence of hypertensive episodes can, of course, not be fully excluded.

In the FLAIR MRI, the absence of small dense lesions confirms the absence of clinically relevant cerebral macroangiopathy. The FLAIR MRI sequence used here has recently been shown to be very sensitive in detecting macrovascular lesions [35]. In addition, one patient initially recruited was excluded because of lesions detected with this sequence. Nevertheless, we cannot exclude the possibility that a stronger magnet might have revealed more macrovascular lesions in the patient group. Moreover previous research has suggested that even microvascular alterations (retinopathy, as also present in most of our patients) might be associated with cerebral atrophy [36].

The metabolic alterations in diabetes mellitus also include down-regulation of insulin-like growth factor-1 in humans (IGF-1) [37]. In rat models, down-regulation of IGF-1 occurs in the early stages of the disease [38]. IGF-1 deficiency leads to neuroaxonal dystrophy [39] and direct neuronal delivery of IGF-1 in streptozotocin induced diabetic rats reversed atrophy of myelinated axons in the sural nerve [40]. In the Laron syndrome associated with inability to generate IGF-1 in humans, global cerebral atrophy has been observed in some patients [41]. Thus, the mild global cerebral atrophy observed in the

present study may also be attributed to changes in the IGF-1 system.

In summary, neither memory function nor hippocampal volume were reduced in Type 1 diabetic patients free from clinically apparent macrovascular complications, which is in contrast to studies with older Type 2 diabetic patients. However, some aspects of cognitive function, namely psychomotor speed and selective attention, were impaired. In addition, an increased amount of CSF, consistent with mild cerebral atrophy, was detected in the patient group. The findings of the current small study support the emerging notion that Type 1 diabetes differs in its impact on brain function and structure from Type 2 diabetes. More research is needed to elucidate the pathophysiological mechanisms involved.

Competing interests

None declared.

References

- Brands AM, Kessels RP, de Haan EH, Kappelle LJ, Biessels GJ. Cerebral dysfunction in type 1 diabetes: effects of insulin, vascular risk factors and blood-glucose levels. *Eur J Pharmacol* 2004; **490**: 159–168.
- Allen KV, Frier BM, Strachan MW. The relationship between type 2 diabetes and cognitive dysfunction: longitudinal studies and their methodological limitations. *Eur J Pharmacol* 2004; **490**: 169–175.
- Squire LR. Memory and the hippocampus a synthesis from findings with rats, monkeys, and humans. *Psychol Rev* 1992; **99**: 195–231.
- Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. *Lancet Neurol* 2004; **3**: 169–178.
- McEwen BS, Reagan LP. Glucose transporter expression in the central nervous system: relationship to synaptic function. *Eur J Pharmacol* 2004; **490**: 13–24.
- McEwen BS, Magarinos AM, Reagan LP. Studies of hormone action in the hippocampal formation: possible relevance to depression and diabetes. *J Psychosom Res* 2002; **53**: 883–890.
- Manolio TA, Kronmal RA, Burke GL, Poirier V, O'Leary DH, Gardin JM *et al*. Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. *Stroke* 1994; **25**: 318–327.
- Araki Y, Nomura M, Tanaka H, Yamamoto H, Yamamoto T, Tsukaguchi I *et al*. MRI of the brain in diabetes mellitus. *Neuroradiology* 1994; **36**: 101–103.
- Pirttila T, Jarvenpaa R, Laippala P, Frey H. Brain atrophy on computerized axial tomography scans: interaction of age, diabetes and general morbidity. *Gerontology* 1992; **38**: 285–291.
- Soininen H, Puranen M, Helkala EL, Laakso M, Riekkinen PJ. Diabetes mellitus and brain atrophy: a computed tomography study in an elderly population. *Neurobiol Aging* 1992; **13**: 717–721.
- Dejgaard A, Gade A, Larsson H, Balle V, Parving A, Parving HH. Evidence for diabetic encephalopathy. *Diabet Med* 1991; **8**: 162–167.
- Lunetta M, Damanti AR, Fabbri G, Lombardo M, Di Mauro M, Mughini L. Evidence by magnetic resonance imaging of cerebral alterations of atrophy type in young insulin-dependent diabetic patients. *J Endocrinol Invest* 1994; **17**: 241–245.
- Den Heijer T, Vermeer SE, Van Dijk EJ, Prins ND, Koudstool PJ, Hofman A *et al*. Diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia* 2003; **46**: 1604–1610.
- Convit A, Wolf OT, Tarshish C, de Leon MJ. Reduced glucose tolerance is associated with poor memory and hippocampal atrophy among normal elderly. *Proc Natl Acad Sci USA* 2003; **100**: 2019–22.
- Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham Heart Study. *Int J Obes Relat Metab Disord* 2003; **27**: 260–268.
- Trocha AK, Schmidtke C, Didjurgeit U, Muhlhauser I, Bender R, Berger M *et al*. Effects of intensified antihypertensive treatment in diabetic nephropathy: mortality and morbidity results of a prospective controlled 10-year study. *J Hypertens* 1999; **17**: 1497–1503.
- Convit A, McHugh P, Wolf OT, De Leon MJ, Bobinski M, De Santi S *et al*. MRI volume of the amygdala: a reliable method allowing separation from the hippocampal formation. *Psychiatry Res Neuroimaging* 1999; **90**: 113–123.
- Convit A, de Leon MJ, Tarshish C, De Santi S, Tsui W, Rusinek H *et al*. Specific hippocampal volume reductions in individuals at risk for Alzheimer's disease. *Neurobiol Aging* 1997; **18**: 131–138.
- Hautzinger M. *Allgemeine Depressions-Skala: ADS*. Weinheim: Beltz 1993.
- Steyer R, Schwenkmezger P, Notz P, Eid M. Testtheoretische Analysen des Mehrdimensionalen Befindlichkeitsfragebogens (MDBF). *Diagnostica* 1994; **40**: 320–328.
- Oswald WD, Fleischmann UM. *Nuernberger Alters Inventar (NAI)*. Goettingen, Germany: Hogrefe 1994.
- Oswald WD, Roth E. *Der Zahlen-Verbindungs-Test (ZVT)*. Goettingen, Germany: Hogrefe 1978.
- Hershey T, Perantie DC, Warren SL, Goldberg BE, Hartlein JL, Black KJ *et al*. Neuroimaging of childhood diabetes: hypoglycemia, memory and hippocampal volumes. *J Internatl Neuropsychol Soc* 2004; **10**: 58.
- Musen G, Lyoo IK, Sparks C, Weinger K, Renshaw PF, Hwang J *et al*. Evidence for reduced gray matter density in patients with type 1 diabetes as measured by magnetic resonance imaging. *64th Scientific Session of the American Diabetes Association (ADA)*, 2004, Abstract 247 OR.
- Ryan CM, Williams TM. Effects of insulin-dependent diabetes on learning and memory efficiency in adults. *J Clin Exp Neuropsychol* 1993; **15**: 685–700.
- Reske-Nielsen E, Lundbaek K, Rafaelsen OJ. Pathological changes in the central and peripheral nervous system of young long-term diabetics. I. Diabetic encephalopathy. *Diabetologia* 1965; **1**: 233–241.
- Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 1994; **125**: 177–188.
- Hershey T, Bhargava N, Sadler M, White NH, Craft S. Conventional versus intensive diabetes therapy in children with type 1 diabetes: effects on memory and motor speed. *Diabet Care* 1999; **22**: 1318–1324.
- Ryan CM, Becker DJ. Hypoglycemia in children with type 1 diabetes mellitus. Risk factors, cognitive function, and management. *Endocrinol Metab Clin North Am* 1999; **28**: 883–900.
- Perros P, Deary IJ, Sellar RJ, Best JJ, Frier BM. Brain abnormalities demonstrated by magnetic resonance imaging in adult IDDM patients with and without a history of recurrent severe hypoglycemia. *Diabet Care* 1997; **20**: 1013–1018.
- Langan SJ, Deary IJ, Hepburn DA, Frier BM. Cumulative cognitive impairment following recurrent severe hypoglycaemia in adult patients with insulin-treated diabetes mellitus. *Diabetologia* 1991; **34**: 337–344.
- Lincoln NB, Faleiro RM, Kelly C, Kirk BA, Jeffcoate WJ. Effect of long-term glycemic control on cognitive function. *Diabet Care* 1996; **19**: 656–658.

- 33 Wredling R, Levander S, Adamson U, Lins PE. Permanent neuropsychological impairment after recurrent episodes of severe hypoglycaemia in man. *Diabetologia* 1990; **33**: 152–157.
- 34 Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complication Trial. *Diabetes* 1997; **46**: 271–286.
- 35 Saleh A, Wenserski F, Cohnen M, Furst G, Godehardt E, Modder U. Exclusion of brain lesions: is MR contrast medium required after a negative fluid-attenuated inversion recovery sequence? *Br J Radiol* 2004; **77**: 183–188.
- 36 Wong TY, Mosley TH Jr, Klein R, Klein BE, Sharrett AR, Couper DJ *et al*. Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. *Neurology* 2003; **61**: 806–811.
- 37 Bereket A, Lang CH, Wilson TA. Alterations in the growth hormone-insulin-like growth factor axis in insulin-dependent diabetes mellitus. *Horm Metab Res* 1999; **31**: 172–181.
- 38 Li JB, Wang CY, Chen JW, Feng ZQ, Ma HT. Expression of liver insulin-like growth factor 1 gene and its serum level in patients with diabetes. *World J Gastroenterol* 2004; **10**: 255–259.
- 39 Schmidt RE, Dorsey DA, Beaudet LN, Parvin CA, Zhang W, Sima AA. Experimental rat models of types 1 and 2 diabetes differ in sympathetic neuroaxonal dystrophy. *J Neuropathol Exp Neurol* 2004; **63**: 450–460.
- 40 Brussee V, Cunningham FA, Zochodne DW. Direct insulin signaling of neurons reverses diabetic neuropathy. *Diabetes* 2004; **53**: 1824–1830.
- 41 Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958–2003. *J Clin Endocrinol Metab* 2004; **89**: 1031–1044.