

Cognitive Ability and Brain Structure in Type 1 Diabetes

Relation to Microangiopathy and Preceding Severe Hypoglycemia

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Type 1 diabetes is associated with chronic hyperglycemia and exposure to intermittent severe hypoglycemia. The long-term cerebral effects of these consequences of diabetes are ill defined. In this study, the history of preceding severe hypoglycemia and the presence of background retinopathy were examined in relation to cognitive ability (neuropsychological test battery) and brain structure (magnetic resonance imaging) in a cross-sectional evaluation of 74 young people with type 1 diabetes. Participants differed by their severe hypoglycemia exposure and degree of diabetic retinopathy and none had previous neuropsychological pathology. Severe hypoglycemia did not influence cognitive ability or brain structure. Background diabetic retinopathy was associated with small focal white-matter hyperintensities in the basal ganglia (33.3 vs. 4.7%, after correction for age, $P = 0.005$) and significant cognitive disadvantage, affecting fluid intelligence ($P = 0.008$, $Eta^2 = 0.14$), information processing ($P = 0.001$, $Eta^2 = 0.22$), and attention and concentration ability ($P = 0.03$, $Eta^2 = 0.09$). In conclusion, recurrent exposure to severe hypoglycemia alone in young people with type 1 diabetes had no detrimental impact on brain structure or function over the duration of diabetes examined. Chronic hyperglycemia (inferred by the presence of background diabetic retinopathy) may affect brain structure and function. *Diabetes* 52:149–156, 2003

Intensified insulin therapy, which can achieve strict glycemic control and reduce the risk of diabetic microangiopathy, is associated with a threefold higher incidence of severe hypoglycemia (1). Protracted severe hypoglycemia is uncommon but may cause

permanent neurological and cognitive deficits. Anecdotal reports have described specific neurological and cognitive deficits following protracted severe hypoglycemia that were associated with localized neuroimaging abnormalities (2–7), predominantly affecting the frontal lobes and deep gray matter, which appear more susceptible to hypoglycemia-induced damage (8). It is undetermined whether recurrent severe hypoglycemia, in the absence of protracted coma, can have long-term deleterious effects on intellectual function. The human brain depends on continuous glucose availability and rapidly malfunctions during hypoglycemia but quickly recovers; a single episode of hypoglycemic coma temporarily impairs intellectual function, but no permanent effects on cognitive ability are evident after 36 h (9). Prospective studies, with an evaluation period of up to a decade, have found that recurrent severe hypoglycemia had no detrimental effect on cognitive function in young people with type 1 diabetes (10–12). However, cross-sectional studies of older adults in whom type 1 diabetes had commenced after adolescence, and who had a longer duration of disease, have demonstrated a modest but significant cognitive decrement associated with the frequency of preceding severe hypoglycemia (13–16). A study of a small subgroup of these subjects, using magnetic resonance imaging (MRI) of the brain, suggested that cortical atrophy was more prevalent in those with a history of frequent exposure to severe hypoglycemia (17).

Cerebral macrovascular disease is increased in type 1 diabetes, and the incidence rises with age (18). Multiple neuropathological abnormalities have been described postmortem in brains of individuals with type 1 diabetes who had end-stage microangiopathy (19), but the abnormalities could not be attributed exclusively to diabetic microangiopathy, because macrovascular disease, hypertension, and uremia coexisted. Thus, whether the development of cerebral microangiopathy is caused by diabetes per se remains speculative. The concept of a multifactorial “diabetic encephalopathy” has been proposed (20), with diabetic microangiopathy, metabolic derangements, and hypertension as contributors (21). The potential relationship between diabetic microangiopathy, cognitive performance, and brain structure has been addressed in a few small studies that were confounded by comorbidity (20,22,23). An increased frequency of high-intensity le-

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CRT, Choice Reaction Time; DCCT, Diabetes Control and Complications Trial; IT, Inspection Time; MRI, magnetic resonance imaging; NART, National Adult Reading Test; PASAT, Paced Auditory Serial Addition Task; SPWML, small punctate white-matter lesion; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

TABLE 1
Characteristics of participants with type 1 diabetes

	No retinopathy	Background retinopathy	<i>P</i>
<i>n</i>	46	25	
Age (years)	26.4 ± 4.6 (26, 20–36)	31.5 ± 6.0 (32, 21–44)	0.23
Sex (male: female)	23:23	14:11	0.63
Secondary education (years)	6.9 ± 2.3 (6, 4–11)	7.3 ± 2.4 (8, 4–11)	0.95
NART (premorbid cognitive ability)	31.9 ± 6.0 (32, 15–42)	32.5 ± 6.6 (33, 16–41)	0.94
HbA _{1c} at time of study (5.0–6.5%)	8.4 ± 1.2	8.9 ± 1.3	0.83
Blood pressure (mmHg)	123/73 ± 14/10	121/74 ± 12/11	0.56
Age at diagnosis of T1DM (years)	9.5 ± 4.4 (9, 1–16)	9.9 ± 4.0 (10, 1–17)	0.67
Duration of diabetes (years)	17.0 ± 4.6 (16, 10–30)	21.6 ± 5.9 (22, 10–31)	0.052
Severe hypoglycemia			
Total lifetime episodes	6.0 (0–200)	4.0 (0–45)	0.86
1st Tertile	0.0 (0–0)	0.0 (0–0)	—
2nd Tertile	5.0 (1–10)	4.0 (1–10)	0.68
3rd Tertile	26.5 (11–200)	24.0 (12–45)	0.67

Data are means ± SD (median, range). T1DM, type 1 diabetes mellitus. HbA_{1c}: nondiabetic range 5.0–6.5% (by high-performance liquid chromatography).

sions of the cerebral white matter (leukoaraiosis) representing foci of ischemia and gliosis (24) were described in a small cohort with a long duration of type 1 diabetes who had microangiopathy, hypertension, and uremia (20), whereas no cerebral MRI abnormalities were observed in another study of subjects who had laser-treated proliferative retinopathy (22). A further neuroimaging study reported an increased frequency of cerebral atrophy in people with type 1 diabetes but was too small to offer clues as to causality (23).

The present study examined a group of young people with type 1 diabetes of relatively long duration, who had developed the disorder during childhood or adolescence, and who may be at greater risk of developing cognitive impairment than those with adult-onset type 1 diabetes (25). This study was designed to ascertain the possible long-term consequences of preceding recurrent severe hypoglycemia, the presence of microvascular disease (as retinopathy), and their interaction on cerebral structure and cognitive performance and to determine whether any correlation existed between structural and functional brain states. This study was not designed to examine the effects of diabetes per se on cognitive function.

Design. The study was cross-sectional in design, and the study protocol was completed as follows: detailed MRI of the brain, neuropsychological test battery, retinal examination, and assessment of preceding severe hypoglycemia. Each component was evaluated and scored blind to all other information.

Subjects. Recruitment criteria were chosen with the aim of obtaining a cohort with a long duration of diabetes (>10 years), sufficient to ensure exposure to the metabolic consequences of interest (severe hypoglycemia and diabetic retinopathy), but without other significant confounding comorbidity. Subjects who had developed type 1 diabetes in childhood or adolescence (age at diagnosis <18 years) and who had attained full intellectual development (aged >20 years) at the time of the study were recruited. An age limit of 45 years was applied to minimize potential confounding effects of aging on cognitive ability and brain structure. Participants either had no evidence of diabetic microvascular complications or had background retinopathy alone. People with more advanced degrees of

retinopathy (Airlie House grading [26] ≥2), including maculopathy, preproliferative, proliferative retinopathy, or previous laser-treated retinopathy, were excluded to minimize the potential confounding influence of visual impairment. The presence of any form of clinical neuropathy and microalbuminuria were also considered exclusion criteria. Other exclusions included hypertension (defined as blood pressure >140/90 mmHg), central nervous system pathology, previous alcohol or drug misuse, or any other multisystem disease known to affect the central nervous system.

A total of 74 individuals with type 1 diabetes were recruited, and 71 participants completed the study protocol, with 3 participants failing to perform the cognitive assessment. The data presented are representative of those who completed the study protocol. The clinical characteristics of the study cohort are summarized in Table 1. Altogether 25 subjects (35%) had background diabetic retinopathy, identified by digital retinal imaging and direct ophthalmoscopy, defined by the presence of two or more microaneurysms in one eye (Airlie House Gratings 1a–1c [26]). Severe hypoglycemia was defined as an episode that required external assistance for recovery, identical to the Diabetes Control and Complications Trial (DCCT) definition (1). Severe hypoglycemia exposure was assessed retrospectively using a validated hypoglycemia questionnaire (27). To improve the accuracy of estimates, participants were requested to discuss their severe hypoglycemia history with relatives or friends before completing questionnaires. Details were recorded of the lifetime total number of episodes, the frequency of occurrence of episodes, and the total number of episodes of convulsions, coma, and other episodes requiring medical assistance to treat the hypoglycemia. Using the above definition, 20 subjects (28%) had never experienced severe hypoglycemia and 51 (72%) had experienced one or more episode (Table 1). Subdividing the cohort by presence of background retinopathy showed a similar level of exposure to severe hypoglycemia between the two subgroups, with a slight excess of preceding severe hypoglycemia in the subgroup with no retinopathy. The participants with established retinopathy were slightly older and tended to have had diabetes of longer duration, although both

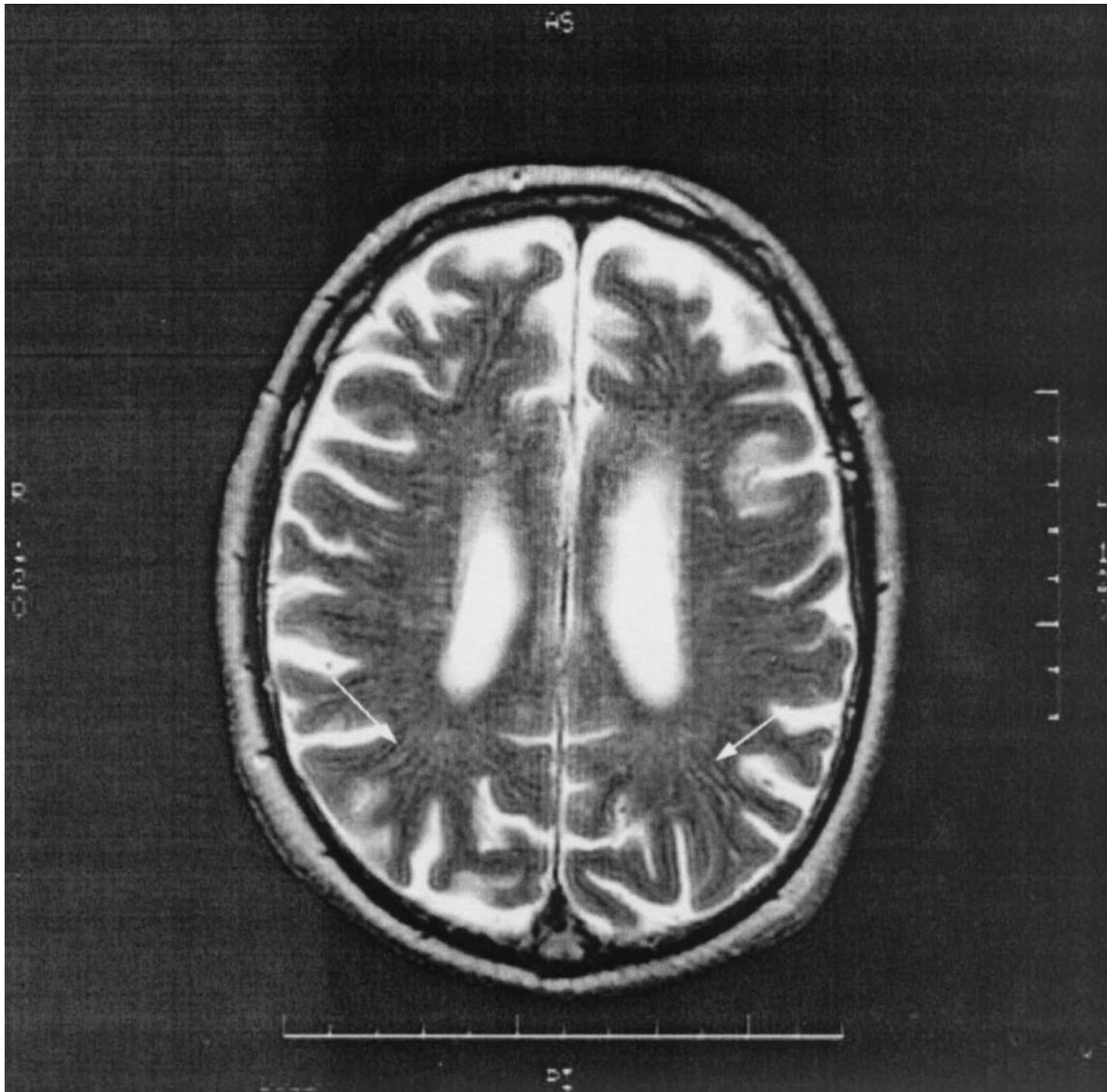


FIG. 1. SPWMLs (enlarged perivascular spaces). This example shows more extensive changes than typical for the diabetic subjects, so as to be more visible.

groups developed type 1 diabetes at a similar age. The subgroups with or without retinopathy were very similar in their duration of education and estimated premorbid cognitive ability.

RESEARCH DESIGN AND METHODS

MRI protocol. MRI examinations of the brain were performed using a 1.0T swap phase encoding (SPE) Magnetom scanner (Siemens, Erlangen, Germany). Following midline localization, two sequences were used to image the whole brain (28). The first scan was a double spin-echo sequence giving simultaneous proton-density and T2-weighted images (relaxation time [TR] = 3,565 ms, echo time [TE] = 20 ms and 90 ms, 31 contiguous 5-mm slices acquired in the Talairach plane, and field of view [FOV] 250 mm) that were used to calculate whole-brain and cerebrospinal fluid volumes using a supervised cluster analysis package (ANALYZE; Mayo Foundation, Rochester, MN). The second scan, for the regional volumetric analysis, was a three dimensional magnetization prepared for rapid-acquisition gradient echo sequence consisting of a 180-inversion pulse followed by a fast low-angle shot collection (Flip angle 12, TR = 10 ms, TE = 4 ms, TI = 200 ms, relaxation time delay time 500 ms, and FOV 250 mm) giving 128 contiguous 1.88-mm thick slices in the coronal plane orthogonal to the Talairach plane. Inhomogeneity corrections were performed on Sun Microsystems workstations using ANALYZE to outline neuroanatomical structures. The temporal lobe and amygdala-hippocampal complex were identified, the areas outlined, and volumes

calculated by summing voxels in the regions of interest. MRI scans were reviewed by an experienced neuroradiologist (J.W.), scored independently, and blinded to clinical factors for the presence of high-intensity white-matter lesions (leukoaraiosis) (29–36). Several scoring systems were used to capture the intensity, distribution, and appearance of white-matter lesions, as no single scale was judged to be an adequate summary (37). MRI scans were also scored for the presence of small punctate white-matter lesions (SPWMLs) that were not accounted for by any of the above rating scales (Fig. 1). A scale of 0–3 (none [0], mild [<10], moderate [10–20], and severe [>20]) was used to quantify SPWMLs, indicating enlarged perivascular spaces in three brain regions (hippocampus, basal ganglia, and centrum semiovale) using the most affected hemisphere. Cerebral atrophy was defined as “central” (i.e., with enlargement of the ventricles) or “gyral” (i.e., with enlargement of the sulci) and rated on a subjective scale of 0–3 (absent [0], mild [1], moderate [2], and severe [3]).

Assessment of neuropsychological function. The neuropsychological test battery was chosen to be sensitive to small-to-moderate differences in ability and to provide an assessment of some major cognitive domains. Trained assessors, blinded to the diabetes characteristics of participants, administered neuropsychological tests in a standardized manner. Blood glucose was measured before the cognitive assessment to exclude prevailing hypoglycemia. The neuropsychological session was rescheduled if antecedent hypoglycemia occurred within the preceding 24 h.

The neuropsychological tests used were as follows:

TABLE 2

Correlation coefficients between measures of exposure to severe hypoglycemia and neuropsychological function (Spearman's rho)

	Performance IQ (WAIS-R)	Frontal and executive function (Borkowski)	Visual information processing (IT)	Psychomotor speed (CRT)	Attention and concentration (PASAT)
Lifetime episodes	-0.009	0.068	-0.068	0.012	-0.129
Frequency of episodes	-0.013	0.063	-0.048	0.011	-0.085
Episodes requiring glucagon	-0.061	0.069	-0.121	0.032	-0.038
Episodes requiring medical care	-0.027	0.044	-0.061	0.014	-0.113
Episodes of coma	0.021	0.121	-0.066	-0.044	-0.089
Episodes of convulsion	-0.023	0.008	-0.086	-0.080	0.044

All correlations, $P > 0.05$.

- The Hospital Anxiety and Depression Scale (38). This was used to assess the potential confounding effects of low mood and anxiety.
- The Wechsler Adult Intelligence Scale-Revised (WAIS-R) (39). The WAIS-R performance IQ subtests are sensitive to disruption by organic brain disease and measure current intellectual performance (fluid intelligence). Picture completion, object assembly, block design, and digit symbol tests were used.
- The National Adult Reading Test (NART) (40). Scoring on the NART is relatively resistant to the effects of organic brain disease, and NART performance correlates more closely with premorbid IQ than demographic variables. NART performance is representative of 'best ever' global cognitive performance (irrespective of age, disease, or time), and in the present study was used as the estimate of premorbid intellectual ability (premorbid IQ, crystallized intelligence).
- Inspection Time (IT) (41). IT was used to assess visual perceptual speed, a component of information processing ability. Participants discriminated between the spatial position (left or right) of two briefly presented vertical lines of different lengths. The stimuli were backward-masked, the presentation duration was varied, and the duration of time required to reliably distinguish the stimulus (85% correct) was termed the participant's 'inspection time.'
- Choice Reaction Time (CRT) (42). CRT was used as a measure of psychomotor speed and complemented IT in assessing information processing ability. Tests measuring 1, 2, 4, and 8 and 8, 4, 2, and 1 CRTs were used.
- Borkowski Verbal Fluency Test (controlled association) (43). This test is thought to assess frontal lobe and executive functions. In this test participants have 60 s to state as many words as possible, beginning with letters of the alphabet specified by the tester.
- Paced Auditory Serial Addition Task (PASAT) (44). PASAT was used to assess the ability to sustain attention and concentration. Participants listened to a numbers list that they were required to add together according to a given rule. After practice, two consecutive trials of 61 numbers were performed with 4 and 2 s between successive digits, respectively.

Statistical analyses. Statistical analysis was performed using SPSS version 10.0 (SPSS, Chicago, IL). The relationship between demographic variables and neuropsychological performance or MRI outcomes (atrophy and white-matter lesions, coded numerically) was examined initially using correlation (Spearman's ρ). Neuropsychological performance was analyzed by domain to reduce the possibility of type I error before subanalysis of individual tests was attempted. Demographic factors correlating with neuropsychological and MRI outcomes were entered into a multivariate linear model (MANCOVA), to take account of potential confounding influences. This technique was used to determine which, if any, of the clinical complications of diabetes influenced brain structure and neuropsychological performance and to estimate the magnitude of their influence (Eta^2). The neuropsychological model used included retinopathy status, severe hypoglycemia exposure (categorized as tertiles of lifetime episodes), and gender as between-subject variables, and premorbid IQ (NART) and duration of diabetes as covariates. The brain volume model used retinopathy status, severe hypoglycemia (as tertiles of lifetime episodes), and gender as between-subject variables and age and intracranial volume as covariates. Parameters were selected on the basis of prior hypotheses and correlates between demographic variables and neuropsychological performance. The interaction between retinopathy and severe hypoglycemia was also explored; diabetes complications were coded into four categories (none, retinopathy alone, hypoglycemia alone, or both complications), and significance was determined using ANOVA with conservative post hoc comparisons (Scheffe).

RESULTS

Cognitive ability

Severe hypoglycemia and neuropsychological performance. No measure of preceding severe hypoglycemia correlated with neuropsychological performance. The correlation coefficients (Spearman's ρ) between estimates of preceding severe hypoglycemia and neuropsychological performance are shown in Table 2.

Background diabetic retinopathy and cognitive performance. The relative neuropsychological performance of those with and without background retinopathy is shown in Table 3, along with the estimated effect size (Eta^2) of background retinopathy and premorbid IQ (NART). Any cognitive difference between these two groups is not a consequence of more education or prior ability, because these variables are very similar in both groups (Table 1). Those subjects who had background retinopathy performed less well across most cognitive domains examined. Retinopathy was associated with comparatively poorer current intellectual performance (WAIS-R performance IQ, $P = 0.008$) of moderate effect size ($\text{Eta}^2 = 0.14$), particularly notable for the Block Design and Digit Symbol Substitution subtests, which assess spatial ability and mental flexibility/psychomotor speed, respectively. Information processing ability (sum of Z scores for CRT and IT) was poorer in those with retinopathy ($P = 0.001$), and the effect size was moderate to large ($\text{Eta}^2 = 0.22$). Both components of the information processing tests were affected: CRT (decision time component $P = 0.003$, $\text{Eta}^2 = 0.17$) and early visual information processing ($P = 0.03$, $\text{Eta}^2 = 0.09$) were comparatively slower. The ability to sustain attention and concentration (PASAT) was also poorer in those who had retinopathy ($P = 0.03$, $\text{Eta}^2 = 0.09$). The presence of retinopathy was not associated with a performance disadvantage on the Borkowski Verbal Fluency Test, a test that is thought to examine frontal lobe and executive functions.

Duality of cerebral insults: chronic hyperglycemia and severe hypoglycemia. The coexistence of background retinopathy and preceding severe hypoglycemia did not result in any additional difference in cognitive ability than that already observed in those with background retinopathy alone (retinopathy \times severe hypoglycemia interaction $F = 0.52$, $P = 0.76$, $\text{Eta}^2 = 0.05$), although the subgroups formed were small (retinopathy alone $n = 8$ vs. severe hypoglycemia and retinopathy $n = 17$).

TABLE 3
Influence of background retinopathy and premorbid intellectual ability (NART) on neuropsychological performance

Neuropsychological domain	No retinopathy		Retinopathy		Effect of retinopathy		Effect of NART
	Mean (SD)	Z score	Mean (SD)	Z score	F	P	
Performance IQ (WAIS-R scaled scores)	43.1 ± 8.0	0.22	37.6 ± 8.2	-0.41	$P = 0.008$, $\text{Eta}^2 = 0.14$	$P < 0.0001$, $\text{Eta}^2 = 0.32$	
Picture completion	9.4 ± 2.9	0.07	8.5 ± 2.4	-0.13	$P = 0.39$, $\text{Eta}^2 = 0.01$		
Block design	12.3 ± 2.5	0.32	9.7 ± 3.3	-0.55	$P < 0.001$, $\text{Eta}^2 = 0.22$		
Object assembly	10.0 ± 3.0	0.07	9.2 ± 2.3	-0.13	$P = 0.44$, $\text{Eta}^2 = 0.01$		
Digit symbol substitution	11.4 ± 2.5	0.19	10.2 ± 2.5	-0.28	$P = 0.04$, $\text{Eta}^2 = 0.07$		
Frontal and executive functions							
Verbal fluency score	43.3 ± 13.0	-0.04	46.4 ± 11.7	0.07	$P = 0.72$, $\text{Eta}^2 < 0.01$	$P = 0.01$, $\text{Eta}^2 = 0.13$	
Information processing							
Inspection time (ms)	46.8 ± 17.9	-0.15	56.2 ± 17.5	0.29	$P = 0.03$, $\text{Eta}^2 = 0.09$	$P = 0.78$, $\text{Eta}^2 < 0.01$	
Median four-choice reaction time (ms)	308.2 ± 43.1	-0.23	346.2 ± 60.2	0.44	$P = 0.003$, $\text{Eta}^2 = 0.17$	$P = 0.13$, $\text{Eta}^2 = 0.05$	
Attention and concentration							
PASAT 2s errors	23.3 ± 10.1	-0.16	28.0 ± 14.2	0.30	$P = 0.03$, $\text{Eta}^2 = 0.09$	$P = 0.009$, $\text{Eta}^2 = 0.14$	

Data are means ± SD, unless otherwise indicated.

Neuroimaging

Abnormalities on neuroimaging were generally at the mild end of the spectrum. High-intensity periventricular white matter lesions, particularly small punctate lesions (Fig. 1), periventricular caps, or pencil-thin rims (Figs. 2A and B) were common and present in one-third of scans. Deep white matter lesions were observed infrequently.

Severe hypoglycemia and brain structure. No significant correlation was identified between any measure of previous exposure to severe hypoglycemia and MRI neuroimaging abnormalities. In particular, no relationship was observed between the presence of high-intensity lesions in the cerebral white matter ($\rho = 0.018$, $P = 0.90$) or cerebral atrophy ($\rho = -0.026$, $P = 0.84$) and any measure of severe hypoglycemia.

Background retinopathy and cerebral abnormalities on MRI. No association was observed among background retinopathy, cerebral atrophy, or brain volumetric measurements (Table 4). The presence of background retinopathy was associated with more frequent SPWMLs in the region of the basal ganglia. One-third (33.3%) of those with background retinopathy had mild basal ganglia periventricular SPWMLs (<10 lesions) compared with 4.7% of those with no retinopathy. The relationship remained statistically significant ($P = 0.01$) after considering the influence of age and gender (MANCOVA), but background retinopathy only accounted for a small proportion of the variance in SPWML scores ($\text{Eta}^2 = 0.09$), and the presence of SPWMLs was not associated with neuropsychological performance. SPWMLs in the hippocampus or centrum semiovale, or a summation of SPWMLs in all areas, were no more frequent in those who had background retinopathy. White matter lesions other than small punctate lesions (i.e., leukoaraiosis), as rated by published scales (29,30,32–36), were no more common in those who had background retinopathy than in those who did not.

Duality of cerebral insults: chronic hyperglycemia, severe hypoglycemia and brain structure. Cerebral atrophy or white matter lesions, in the form of SPWMLs or leukoaraiosis, were no more prevalent in those who had background retinopathy and who had also experienced severe hypoglycemia than in those with only background retinopathy.

DISCUSSION

In the present study, no significant relationship was identified between previous exposure to severe hypoglycemia and cognitive ability. This is consistent with the observations of the DCCT (10,12) and the Stockholm Diabetes Intervention Study (SDIS) (11), both of which evaluated cognitive function in young adults who had been exposed to recurrent severe hypoglycemia. However, retrospective cross-sectional studies in adults with type 1 diabetes (13–16) have revealed modest decrements in cognitive function, directly related to the frequency of previous recurrent severe hypoglycemia, in people who developed type 1 diabetes in adulthood and who were older than the participants of the present study. This could imply that the aging brain may be more susceptible to the effects of severe hypoglycemia. The apparently reassuring findings with respect to exposure to severe hypoglycemia from the present study do not exclude effects on other domains of

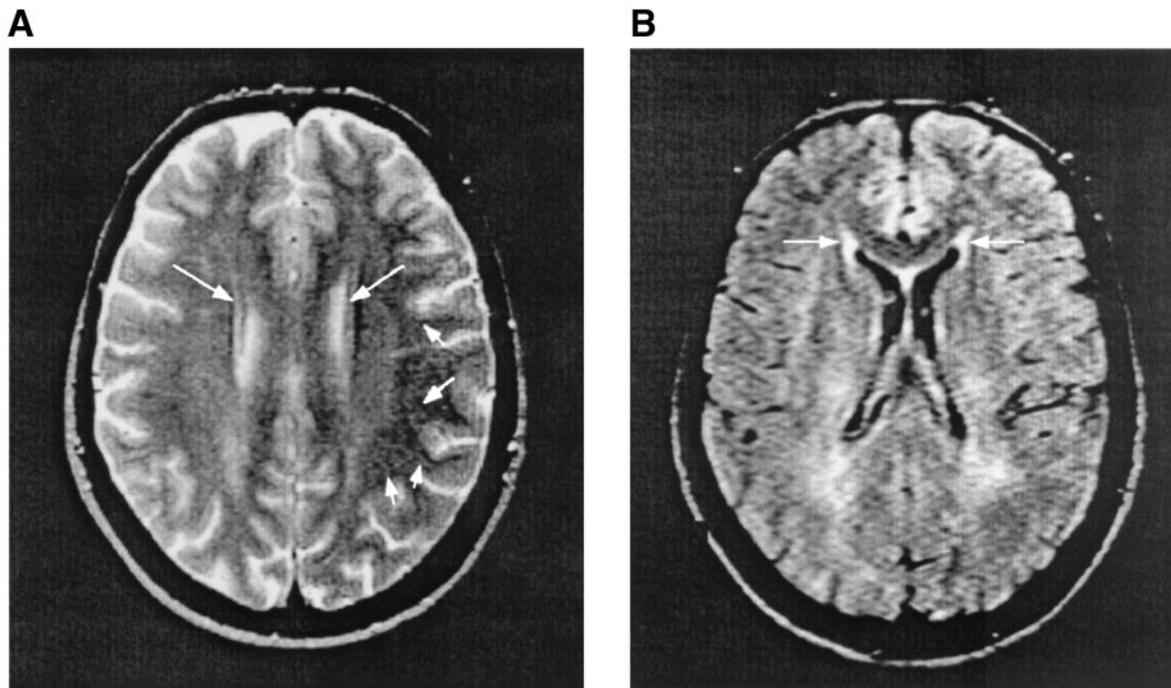


FIG. 2. *A*: A T2-weighted image from a diabetic patient. Note the minimal rim of increased signal around the lateral ventricles (arrow) and the very few enlarged perivascular spaces in the deep white matter (arrowheads). *B*: Fluid attenuated inversion recovery (FLAIR) image from the same patient showing the rim of periventricular high signal (arrows) more clearly.

cognitive ability because the assessment of cognition was not comprehensive; learning, memory ability, abstract reasoning, and a detailed examination of executive functions were not examined. Based on our previous findings, the focus of the present study was on general cognitive ability and information processing (14).

In the present study, structural abnormalities of the brain were not observed in association with a history of preceding severe hypoglycemia. No relationship was identified between the frequency of previous severe hypoglycemia and cerebral atrophy, in contrast to the observations of an earlier study (17), which examined a small number of older participants recruited from a larger cohort (14,27) who had developed type 1 diabetes in adulthood. In addition, in analyzing these earlier results (17), differences between the incidence of microvascular disease in the study groups were not considered (82% in those previously exposed to severe hypoglycemia vs. 55% in those who were not exposed to severe hypoglycemia). These differences may underlie the apparent disparity with the results of the present study, which suggest that recurrent severe hypoglycemia may not be detrimental to the

brain, at least in young adults <45 years of age who do not have established microangiopathy. This reassurance cannot at present be applied to older people with type 1 diabetes or to those with a longer duration of the disorder.

A significant association was found between the presence of background diabetic retinopathy and cognitive ability, which remained robust when between-subject factors and covariates (age, gender, premorbid IQ, and duration of diabetes) were considered. The subgroup that had background diabetic retinopathy performed less well on cognitive tests of fluid intelligence, information processing speed, and the ability to maintain attention and concentration. The magnitude of the difference observed in cognitive performance was moderate (0.4–0.7 SD), i.e., approximately equivalent to 10 IQ points, and was similar to that observed by other studies that examined the relationship between microangiopathy and cognition (20,45). However, the differences observed in cognitive performance in the present study may be evident at a lesser degree of cumulative lifetime glycemic exposure (46). The reasons for this are unclear but may reflect differences in the sensitivity of neuropsychological test batteries to hyperglycemia-asso-

TABLE 4
Influence of background retinopathy and age on brain volumes (adjusted for intracranial volume by MANCOVA)

Brain volume (cm ³)	No retinopathy	Retinopathy	Effect of retinopathy	Effect of age
Whole brain	1,261 (1,242–1,281)	1,250 (1,225–1,275)	$P = 0.76$, $\text{Eta}^2 < 0.01$	$P = 0.04$, $\text{Eta}^2 = 0.07$
Lateral ventricles	22.3 (20–25)	17.9 (15–21)	$P = 0.14$, $\text{Eta}^2 = 0.04$	$P = 0.50$, $\text{Eta}^2 < 0.01$
Right temporal lobe	77.4 (75–79)	74.6 (72–77)	$P = 0.08$, $\text{Eta}^2 = 0.05$	$P = 0.80$, $\text{Eta}^2 < 0.01$
Left temporal lobe	72.4 (71–74)	72.5 (70–75)	$P = 0.44$, $\text{Eta}^2 < 0.01$	$P = 0.99$, $\text{Eta}^2 < 0.01$
Right amygdala-hippocampal complex	4.5 (4.3–4.6)	4.3 (4.1–4.5)	$P = 0.23$, $\text{Eta}^2 = 0.02$	$P = 0.005$, $\text{Eta}^2 = 0.12$
Left amygdala-hippocampal complex	4.4 (4.2–4.6)	4.3 (4.0–4.5)	$P = 0.39$, $\text{Eta}^2 = 0.01$	$P = 0.006$, $\text{Eta}^2 = 0.12$

Data are mean volume (95% CI) unless otherwise indicated.

ciated cognitive change and the different cognitive domains assessed. The mechanism by which background retinopathy may confer these differences in cognitive ability is unknown. Differences in visual function were considered as being potentially responsible for the differences in ability associated with retinopathy, yet the visual component of the information processing pathway (as measured by P100 latency) is unaffected by background retinopathy (47). It is more likely that the presence of diabetic retinopathy (which infers that microangiopathy is present in other tissues) is a surrogate marker of preceding suboptimal control of diabetes with chronic hyperglycemia.

High-intensity white-matter lesions (leukoaraiosis) represent areas of increased water content, gliosis, and demyelination within white matter (24) and are thought to signify foci of microvascular ischemia (48). The SPWMLs of the type that were associated with background retinopathy in this study are thought to correspond to enlarged perivascular spaces, in keeping with diabetic microangiopathy in other tissues. The intracranial circulation, with the exception of the ophthalmic artery, was previously thought to be spared by diabetic microangiopathy. To our knowledge, the association observed in the present study between background retinopathy and SPWMLs in the basal ganglia has not been previously reported and suggests that microangiopathy affects cerebral microvessels beyond the confines of the ophthalmic artery. Basal ganglia abnormalities have been previously observed in young people with type 1 diabetes, with infarction in association with microvascular complications (49) and hemorrhage in association with ketoacidosis (50,51). The vascular supply to the basal ganglia is via an end-arterial system, similar to the retinal circulation, which may therefore explain their apparent vulnerability.

This observed association between background retinopathy and SPWMLs is consistent with other observations associating retinal vascular abnormalities with white-matter lesions on cranial MRI scans. Hypertensive retinopathy is associated with cerebral high-intensity white-matter lesions (52), implying that retinal microangiopathy is a marker of diffuse cerebral microangiopathy in hypertension. Despite the association observed in the present study between background retinopathy and SPWMLs, the presence of these white-matter lesions was not associated with cognitive ability. This may imply that diabetic retinopathy and SPWMLs do not in fact represent an identical histopathological abnormality. Alternatively, the pathogenesis of diabetic retinopathy and SPWMLs may be similar, with nonexudative retinopathy representing an early manifestation and SPWMLs (enlarged perivascular spaces) indicating more advanced damage. A further explanation is offered by the difference in sensitivity for the detection of microangiopathy provided by cerebral magnetic resonance imaging when compared with ophthalmoscopy and digital retinal imaging. The pathognomonic lesion of background diabetic retinopathy, the microaneurysm, is a few microns in size, whereas the voxel size utilized in MRI neuroimaging protocols is several orders of magnitude greater.

Irrespective of the association between background retinopathy and structural brain abnormalities, the cognitive differences observed in the subgroup with established

background diabetic retinopathy is likely to have a vascular etiology. Functional MRI studies suggest that cerebrovascular responsiveness is important during normal cognition, as discrete changes in regional cerebral blood flow occur during cognitive tasks (53). Long-duration type 1 diabetes complicated by retinopathy has been shown to be associated with impaired cerebrovascular responsiveness (54), and it is possible that such a mechanism may be associated with the differences in cognitive ability observed in the present study. In addition, the results of the present study support the concept of a "microvascular-mediated" effect on cognitive function in people with diabetes of long duration, as a contributory factor in the pathogenesis of a "diabetic encephalopathy."

An interaction between multiple complications of diabetes and cognitive performance has been previously reported. Ryan et al. (45) identified an association between poorer cognitive performance and peripheral neuropathy in adults who had developed type 1 diabetes in childhood or adolescence, although no direct detrimental effect of severe hypoglycemia alone was detected. A significantly greater degree of cognitive dysfunction was observed when peripheral neuropathy coexisted with a history of previous exposure to recurrent severe hypoglycemia. The present study did not identify any greater difference in cognitive ability in those who had background retinopathy and a history of exposure to recurrent severe hypoglycemia when compared with those who had background retinopathy alone. However, the numbers constituting the subgroups ($n = 8$ vs. $n = 17$) for this analysis were small, and no firm conclusions regarding the presence or absence of an interaction among microangiopathy, severe hypoglycemia, and cognitive ability can be drawn from the present study.

In conclusion, the present study indicates that neither structural abnormalities of the brain of known clinical significance nor cognitive impairment were common in young adults with type 1 diabetes. SPWMLs of uncertain clinical significance were observed more frequently in the brains of those with the microvascular complication of retinopathy and may be related to chronic hyperglycemia. In people with type 1 diabetes, the exposure to chronic hyperglycemia and the development of generalized microangiopathy may have a more detrimental effect on the brain than recurrent exposure to severe hypoglycemia. Prospective studies are required to validate the above findings, which, if substantiated, will have important implications for the clinical management of diabetes in routine practice.

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