Influence of an Early-Onset Age of Type 1 Diabetes on Cerebral Structure and Cognitive Function

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OBJECTIVE — Children who develop type 1 diabetes before age 7 years (early-onset diabetes; EOD) have comparatively poorer cognitive abilities. Whether this relates to psychosocial consequences of chronic illness or organic factors related to diabetes and its complications remains unresolved. We hypothesized that if differences in neuroradiological structure and cognitive ability coexisted in those who had EOD, then an organic component to their etiology was likely.

RESEARCH DESIGN AND METHODS — A cohort of 71 young adults with long-duration type 1 diabetes diagnosed during childhood or adolescence participated in a cross-sectional evaluation of cognitive ability (neuropsychological test battery) and brain structure (magnetic resonance imaging). Diabetes onset age, preceding severe hypoglycemia exposure, retinopathy status, and diabetes duration were examined as potential correlates of cognitive and neuroradiological differences. No participants had previous neuropsychological pathology.

RESULTS — In EOD participants ($n = 26$), current intellectual ability (Wechsler Adult Intelligence Scale−Revised performance IQ; $P = 0.03$) and information processing ability (Choice Reaction Time; $P = 0.006$) were comparatively poorer than was observed in those with later-onset diabetes ($n = 45$). Furthermore, lateral ventricular volumes were 37% greater ($P = 0.002$) and ventricular atrophy was more prevalent (61 vs. 20%; $P = 0.01$) in the EOD group than in those who had later-onset type 1 diabetes.

CONCLUSIONS — An early childhood onset of type 1 diabetes was associated with mild central brain atrophy and significant differences in intellectual performance in adulthood, implying that neurodevelopment may be adversely affected by EOD. The differences observed in brain structure support an organic contribution to their etiology but do not exclude a coexistent contribution of psychosocial factors.

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Optimal intellectual development may be compromised by early childhood onset type 1 diabetes. The diabetes-related factor most consistently related to later intellectual ability is the onset age of type 1 diabetes; children developing the disorder in early childhood are more likely to score relatively poorly on cognitive tests, independent of diabetes duration. Ack et al. (1) first identified an association between early-onset type 1 diabetes (EOD) and comparatively lower general intelligence test scores; children with diabetes averaged 10 IQ points lower than their siblings. Subsequent studies identified small-to-moderate permanent differences in nonverbal (2–5) and verbal (6) intelligence, information processing (3,7–9), visuospatial ability (3–5), attention (7–11), executive function (7,9,12), and learning and memory ability (2,3,7). Prospective evaluation has confirmed that EOD independently influences verbal and nonverbal intelligence, attention, psychomotor speed, and executive functions (6,9). Some researchers have suggested that the differences in intellectual ability may reflect chronic hyperglycemia, severe hypoglycemia, or other diabetes-related organic factors, whereas others have proposed psychosocial factors relating to school attendance (13) and behavior (14) as potential causes. However, the pathogenesis of differences in intellectual ability associated with EOD remains uncertain.

The present study aimed to establish whether cognitive performance differences associated with EOD were associated with coexistent structural brain differences. We hypothesized that if structural brain differences were more prevalent in EOD patients relative to those who developed diabetes later in life, then an organic contribution to their etiology was likely.

RESEARCH DESIGN AND METHODS

— This cross-sectional protocol consisted of four separate components, each evaluated by an assessor blind to all other information, completed in the following order: cranial magnetic resonance, assessment of cognitive ability, retinal examination, and assessment of preceding severe hypoglycemia exposure.

Using the diabetes clinic database, we identified 96 individuals who had devel-

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Abbreviations: CRT, Choice Reaction Time; EOD, early-onset type 1 diabetes; LOD, later-onset type 1 diabetes; 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; WML, white matter lesion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1 —*Clinical characteristics of subjects with type 1 diabetes*

	Onset age ≤7 years	Onset age >7 years	*P*
n	26	45	—
Age (years)	5.2 ± 4.6 (23, 20–36)	29.9 ± 5.6 (30, 20–44)	<0.0001
Sex (male:female)	13:13	24:21	0.79
Secondary education (years)	7.0 ± 2.0 (6, 4–10)	7.1 ± 2.5 (6, 4–11)	0.82
NART (premorbid intellectual ability)	32.8 ± 5.4 (33, 21–41)	31.8 ± 6.6 (32, 15–42)	0.52
HbA_{1c} (%)	8.3 ± 1.1	8.7 ± 1.3	0.20
Blood pressure (mmHg)	122/72 ± 11/10	122/74 ± 14/10	0.94
Age at diagnosis of type 1 diabetes (years)	5.0 ± 2.3 (5.5, 1–7)	12.2 ± 2.4 (12, 8–17)	<0.0001
Duration of diabetes (years)	20.1 ± 5.2 (18.5, 13–31)	17.7 ± 5.5 (16, 10–29)	0.07
Background retinopathy (% with BDR)	23	42	0.10
Severe hypoglycemia			
Median total episodes (% exposed, range)	7.0 (77, 0–200)	4.0 (69, 0–100)	0.48
Median total coma episodes (% exposed, range)	2.0 (65, 0–40)	0.0 (49, 0–9)	0.26
Median total seizures (% exposed, range)	0.0 (46, 0–30)	0.0 (33, 0–6)	0.25

Data are means ± SD (median, range) unless otherwise noted. The HbA_{1c} nondiabetic range was 5.0–6.5% (by high-performance liquid chromatography). BDR, background diabetic retinopathy.

oped type 1 diabetes in childhood or adolescence and who matched recruitment criteria. After a telephone interview, 16 individuals declined to participate and 6 did not fulfill study criteria. The remaining 74 individuals were recruited into the study between August 1997 and August 1999. Data from the 71 participants who completed the study protocol are discussed here. The subjects' clinical characteristics are presented in Table 1. The EOD group ($n = 26$) had developed type 1 diabetes before age 7 years, whereas the remainder, placed in the later-onset diabetes (LOD) group ($n = 45$), had developed diabetes between ages 7 and 17 years. Inclusion and exclusion criteria included no clinical diabetic retinopathy or background retinopathy only (Airlie House grading 1a−1c), diabetes duration >10 years (ensuring exposure to metabolic consequences), age <45 years (to minimize aging as a confounder), and the absence of clinical neuropathy, microalbuminuria, hypertension (blood pressure >140/90 mmHg), previous central nervous system pathology, alcohol or drug misuse, or multisystem disease known to affect the central nervous system.

Informed consent was obtained from participants, and the protocol was executed in accordance with the Helsinki Declaration (1996 revision). Severe hypoglycemia was defined as an episode that required external assistance for recovery, consistent with the Diabetes Control and Complications Trial criteria (15). A validated hypoglycemia questionnaire (16) was used to retrospectively determine exposure. Ophthalmoscopy and digital retinal imaging defined retinopathy status.

Definition of EOD

The present study defined EOD as diabetes diagnosed before age 7 years. In other cognitive ability studies of children with type 1 diabetes, EOD onset has been variously defined as occurring anywhere from age 4 to age 7 years (1), with little reference for preferences (2–12). Magnetic resonance imaging (MRI) neurodevelopmental studies have demonstrated that adult brain volumes are attained by age 7–10 years (17). We selected the seventh birthday as our definition, as adult gray matter volumes could have been attained in LOD participants prior to diagnosis. The lower margin of the 7- to 10-year-old age bracket was selected to provide comparability between present observations and published literature. One prospective study (6) and several cross-sectional studies (2,10) have used similar definitions.

MRI

A 1.0T SPE Magnetom scanner (Siemens, Erlangen, Germany) was used. After midline localization, two sequences imaged the whole brain (18). The first double spin-echo sequence produced simultaneous proton-density and T2-weighted images (reception time [TR] = 3,565 ms; echo delay time [TE] = 20 and 90 ms; 31 contiguous 5-mm slices acquired in the Talairach plane; field of view [FOV] = 250 mm) for whole-brain and cerebrospinal fluid volume calculations using a supervised cluster analysis package (ANALYZE; Mayo Foundation, Rochester, MN). The second regional volumetric scan was a three-dimensional magnetization prepared for a rapid-acquisition gradient echo sequence consisting of an 180 inversion pulse followed by a fast low-angle shot collection (flip angle 12; TR = 10 ms; TE = 4 ms; time for inversion [TI] = 200 ms; relaxation time delay time = 500 ms; 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 Microsystem workstations using ANALYZE to outline neuroanatomical structures. Intracranial, whole-brain, lateral ventricle, temporal lobes, and amygdalohippocampal complex volumes were calculated by summing voxels. MRI scans were independently scored by an experienced neuroradiologist (J.W.) blinded to clinical factors for the presence of high-intensity white matter lesions (WMLs; e.g., leukoaraiosis) (19–26) and cerebral atrophy (20–26), defined as ventricular (i.e., ventricular enlargement) or gyral (i.e., sulcal enlargement) and rated on a scale of 0–3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe). High-intensity WMLs (leukoaraiosis), abnormalities detected on T2-weighted magnetic resonance images representing increased water content, gliosis, and demyelination, are thought to signify focal microvascular

ischemia (27). Several scoring systems were used to capture the intensity, distribution, and appearance of WMLs, as no single scale was judged to be an adequate summary (28). MRI scans were also scored for the presence of small punctate WMLs (SPWMLs), representing enlarged perivascular spaces (typically <1 mm diameter) that were frequently observed but unaccounted for by other rating scales. A scale of 0–3 (0 = no lesions, 1 = mild or <10 lesions, 2 = moderate or 10–20 lesions, 3 = severe or >20 lesions) was used to quantify SPWMLs in three brain regions (hippocampus, basal ganglia, and centrum semiovale) using the most affected hemisphere.

Assessment of intelligence and cognitive ability

The cognitive test battery was selected on the basis of previous observations (29), weighted toward the assessment of current intellectual performance and information processing, and designed to be sensitive to mild-to-moderate cognitive changes. The assessment was not all-encompassing; frontal and executive functions were not assessed in depth, and memory and learning ability were not evaluated. Trained assessors blinded to participants' diabetes characteristics administered the tests in a standardized manner. Assessment was rescheduled if antecedent hypoglycemia episode occurred within the preceding 24 h. The tests used were as follows:

- *Hospital Anxiety and Depression Scale* (30). Mood and anxiety were assessed as potential confounders.
- *Wechsler Adult Intelligence Scale—Revised (WAIS-R)* (31). Organic brain disease disrupts WAIS-R performance IQ subtests that measure current intellectual performance (fluid intelligence). The picture completion, object assembly, block design, and digit symbol tests were used.
- *National Adult Reading Test (NART)* (32). Performance on this test is relatively resistant to the effects of organic brain disease. NART performance represents "best ever" global cognitive performance, irrespective of age, disease, or time. NART scores were used to estimate prior intellectual ability.
- *Inspection Time* (33). This test 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 markedly different lengths. Stimuli were backward masked, and their duration varied using an adaptive staircase algorithm. The duration required to reliably distinguish stimuli (85% correct) was termed the "inspection time."
- *Choice Reaction Time (CRT)* (34). CRT was used to measure psychomotor speed and complemented inspection time in assessing information-processing ability. The one, two, four, and eight and eight, four, two, and one CRTs were measured in that order. A one-choice is simple reaction time.
- *Borkowski Verbal Fluency Test* (35). This test for controlled association was used to assess frontal lobe and executive functions. Participants have 60 s to state as many words as possible beginning with the letters of the alphabet specified by the tester.
- *Paced Auditory Serial Addition Task (PASAT)* (36). The PASAT was used to assess sustained attention and concentration. Participants listened to a list of numbers that they were then required to add together according to a given rule. After practice, two consecutive 61-number trials were performed with fours and twos between successive digits, respectively.

Statistical analyses

SPSS Vers. 10.0 (SPSS, Chicago, IL) was used. The relations among demographic variables, cognitive performance, brain volumes, and MRI appearances (cerebral atrophy and high-intensity WMLs coded numerically) were examined using Spearman's rank correlation. Cognitive and information processing performance was analyzed by ability-related domains to minimize type 1 errors before subanalysis. Multivariate linear models (MANCOVA) were constructed based on prior hypotheses and correlates among demographic variables, cognitive performance, and brain volumes. MANCOVA was used to determine whether diabetes onset age (coded as EOD or LOD) or other diabetes-related factors (e.g., severe hypoglycemia, retinopathy, diabetes duration) influenced cognitive performance or brain structure and to estimate the magnitude of influence (Eta^2). The cognitive model included sex, background, diabetic retinopathy status (present or absent), and diabetes onset age-group (EOD or LOD) as between-subject variables and prior IQ (assessed by the NART), age, diabetes duration, and severe hypoglycemia (log-transformed total lifetime episodes) as covariates. The brain volume model included intracranial volume as an additional covariate. The relation between diabetes-related variables and cerebral atrophy (present or absent) or WMLs (present or absent) was analyzed by binary logistic regression. The model included sex, age, diabetes onset age-group (EOD or LOD), and retinopathy status (present or absent). MANCOVA was used to determine whether brain volumes influenced cognitive performance; sex was entered as a between-subjects factor with brain volumes of interest as covariates. The relation between subjectively rated MRI abnormalities (atrophy, SPWMLs, and leukoaraiosis) and cognitive ability was examined by simple correlation.

RESULTS

Cognitive ability

Prior intellectual ability (assessed by the NART; $F = 7.9$, $P < 0.0001$; higher IQ better), retinopathy status ($F = 6.3$, $P < 0.0001$; background retinopathy poorer), sex ($F = 3.8$, $P < 0.01$), and diabetes onset age-group ($F = 3.0$, $P = 0.03$; EOD poorer) were identified as independent predictors of cognitive ability on multivariate analysis. Preceding severe hypoglycemia ($F = 0.64$, $P = 0.64$) and diabetes duration ($F = 1.0$, $P = 0.41$) did not independently influence cognitive ability. The associations among retinopathy status, severe hypoglycemia, cognitive ability, and brain structure have been reported elsewhere (37).

Table 2 summarizes subjects' cognitive performance. Nonverbal intelligence ability was poorer in EOD subjects (WAIS-R performance IQ score), in whom small-to-moderate performance differences were observed. These related primarily to performance on the block design subtest, which assesses spatial ability. Information processing ability (sum of *Z* scores of CRT and Inspection Time tests) was poorer in EOD subjects. Significant differences in simple and CRT (decision time component) were observed. Early visual perceptual speed (Inspection Time test), sustained attention and concentration (PASAT), and frontal and executive functions (Borkowski Verbal

Table 2 —*Influence of diabetes onset age and prior intellectual ability on cognitive and information processing abilities*

	Diabetes onset age					
	Early-onset group	Later-onset group	Effect	Early-onset group (*Z* score)	Later-onset group (*Z* score)	Effect of prior intellectual ability
Performance IQ (WAIS-R scaled scores)	37.3 (32.1–41.6)	41.7 (39.7–45.8)	$P = 0.03$, $Eta^2 = 0.09$	−0.56	0.13	$P < 0.0001$, $Eta^2 = 0.37$
Picture completion	8.3 (6.7–10.0)	9.3 (8.3–10.3)	$P = 0.20$, $Eta^2 = 0.03$	−0.38	0.14	$P < 0.0001$, $Eta^2 = 0.36$
Block design	9.5 (7.9–11.0)	11.7 (10.8–12.7)	$P = 0.03$, $Eta^2 = 0.08$	−0.66	0.14	$P < 0.0001$, $Eta^2 = 0.39$
Object assembly	9.8 (7.9–11.7)	9.4 (8.3–10.5)	$P = 0.99$, $Eta^2 < 0.01$	−0.04	−0.04	$P = 0.003$, $Eta^2 = 0.14$
Digit symbol substitution	9.7 (8.1–11.3)	11.3 (10.3–12.3)	$P = 0.19$, $Eta^2 = 0.03$	−0.44	0.14	$P = 0.001$, $Eta^2 = 0.16$
Frontal and executive functions (verbal fluency score)	43.6 (34.4–52.7)	44.6 (38.7–50.4)	$P = 0.83$, $Eta^2 = < 0.01$	−0.07	0.01	$P = 0.02$, $Eta^2 = 0.10$
Information processing ability						
Inspection time (ms)	51 (38–63)	53 (45–61)	$P = 0.61$, $Eta^2 < 0.01$	0.15	0.04	$P = 0.54$, $Eta^2 = 0.01$
Simple reaction time (ms)	332 (300–364)	273 (253–293)	$P = 0.012$, $Eta^2 = 0.12$	−0.72	0.26	$P = 0.33$, $Eta^2 = 0.02$
Four-choice reaction time (ms)	366 (335–396)	305 (285–325)	$P = 0.006$, $Eta^2 = 0.13$	−0.84	0.31	$P = 0.09$, $Eta^2 = 0.05$
Attention and concentration ability (PASAT 2*s* series errors)	23.2 (15.3–31.1)	24.5 (19.4–21.5)	$P = 0.41$, $Eta^2 = 0.01$	0.10	−0.01	$P = 0.006$, $Eta^2 = 0.13$

Data are means (95% CI). Prior intellectual ability determined by NART.

Fluency Test) appeared unaffected by diabetes onset age. No significant interaction was observed between EOD and other diabetes-specific factors; background retinopathy and EOD did not interact to influence cognitive ability ($F = 0.71$, $P = 0.59$). Sex independently influenced performance IQ ($P = 0.03$, $Eta^2 = 0.09$; male subjects poorer) and CRT score ($P = 0.006$, $Eta^2 = 0.14$; female subjects poorer). No statistical interaction between sex and diabetes onset age-group was observed.

Neuroimaging

MRI abnormalities were generally mild. High-intensity periventricular WMLs were frequent and deep WMLs were infrequent.

EOD and macroscopic MRI abnormalities. Table 3 summarizes subjectively rated MRI scan abnormalities. Mild-to-moderate ventricular atrophy was common and significantly more prevalent in EOD subjects. Qualitatively rated gyral atrophy was uncommon and unrelated to diabetes onset age. Hippocampal SPWMLs were more frequent in EOD subjects, although SPWMLs in other brain regions or their total number did not differ between groups. The prevalence of leukoaraiosis did not consistently differ between the EOD and LOD groups, although it appeared significantly greater in EOD subjects by the Wahlund rating scale (21).

EOD and brain volumes. Diabetes onset age independently influenced brain volumes ($F = 2.4$, $P = 0.04$). Lateral ventricular volume was 37% greater in EOD subjects. After considering covariates, no other significant regional brain volume differences were observed (Table 3).

Relation between cognitive ability and brain structure

Macroscopic MRI abnormalities and cognitive ability. No correlation was observed between subjectively rated MRI abnormalities (brain atrophy, SPWMLs, or leukoaraiosis) and cognitive or information-processing performance.

Brain volumes and cognitive ability. In general, larger brain volumes equated to superior cognitive performance. Whole-brain volume influenced sustained attention and concentration ability (PASAT; $P = 0.008$, $Eta^2 = 0.10$; larger brain better), information processing speed (mean

Table 3 —*Influence of diabetes onset age-group on subjectively rated macroscopic MRI scan appearances and brain volumes*

	Early-onset group	Later-onset group	Effect of diabetes onset age-group
Ventricular atrophy (% of scans)			
Total	61	20	OR = 4.6, $P = 0.01$*
Mild	50	13	—
Moderate	11	7	—
Gyral atrophy (% of scans)	9	7	NS*
High-intensity WMLs (% of scans)			
Wahlund	59	24	OR = 4.5, $P = 0.007$*
Longstreth	55	53	NS*
Van Swieten (superficial/deep WMLs)	0/0	2/2	NS/NS*
Breteler	18	27	NS*
Fazekas (superficial/deep WMLs)	55/0	60/18	NS/NS*
Shimada	0	11	NS*
Mirsen (superficial/deep WMLs)	1/0	42/9	NS/NS*
Small punctate WMLs (% of scans)			
Hippocampal	14	2	0.03*
Basal ganglia	5	20	0.38*
Centrum semiovale	9	22	0.08*
% with punctate WMLs	18	40	0.17*
Brain volume (cm^3)			
Whole brain	1,270 (1,244–1,296)	1,258 (1,240–1,275)	$F = 0.58$, $P = 0.45$, $Eta^2 = 0.01$†
Lateral ventricle	24.5 (21.4–27.6)	17.9 (15.8–20.0)	$F = 11.1$, $P = 0.002$, $Eta^2 = 0.16$†
Right temporal lobe	76 (74–79)	76 (75–78)	$F = 0.01$, $P = 0.92$, $Eta^2 < 0.01$†
Left temporal lobe	72 (69–74)	73 (71–75)	$F = 0.48$, $P = 0.49$, $Eta^2 = 0.01$†
Right amygdalohippocampal complex	4.3 (4.0–4.5)	4.4 (4.2–4.6)	$F = 0.87$, $P = 0.35$, $Eta^2 = 0.02$†
Left amygdalohippocampal complex	4.2 (4.0–4.5)	4.3 (4.2–4.5)	$F = 0.41$, $P = 0.53$, $Eta^2 = 0.01$†

Data are *n* (range). *Determined by binary logistic regression; †determined by multiple ANCOVA. NS, nonsignificant onset age-group effect in the final logistic regression model. OR, odds ratio.

median four CRT; $P = 0.050$, $Eta^2 = 0.07$; larger brain better), and performance IQ (picture completion [$P = 0.03$, $Eta^2 = 0.07$] and block design [$P = 0.03$, $Eta^2 = 0.07$] subtest scores were superior in those with larger brains). Larger temporal lobes equated to better sustained attention and concentration ability (PASAT; $P = 0.01$, $Eta^2 = 0.19$), faster information processing speed (mean median four CRT; $P = 0.03$, $Eta^2 = 0.08$), and superior performance IQ (picture completion [$P = 0.002$, $Eta^2 = 0.14$] and block design [$P = 0.01$, $Eta^2 = 0.10$] subtest scores were superior in those with larger lobes). Ateral ventricular and amygdalohippocampal volumes did not significantly influence cognitive performance.

CONCLUSIONS

Cognitive ability and EOD

The early childhood development of type 1 diabetes was associated with lower nonverbal intelligence ability (WAIS-R performance IQ, 0.7 SD difference) and slower psychomotor speed (reaction time, 1.0 SD difference) in adulthood, independent of other factors that influenced cognitive performance. The specific cognitive abilities affected were consistent with those previously observed, although varied EOD definitions hinder direct comparisons: lower nonverbal intelligence scores (WAIS-R performance IQ) (2–5) and slower information processing (3,7–9) have been reported, although not consistently (38). Other abilities examined in the present study (visual perceptual speed, frontal and executive functions, and sustained attention and concentration ability) were not significantly influenced by diabetes onset age. Differences in attention (3,8,9) and executive function have been previously associated with early childhood diabetes onset (7,9,12). Discrepancies may reflect study and control group heterogeneity, sample size, the varied psychometric instruments used to detect performance differences, and diverse definitions of EOD.

The NART reliably estimates maximum adult intellectual attainment (crystallized intelligence) when intellectual development occurs in the absence of childhood pathology (32). NART scores are relatively resistant to organic brain disease throughout adulthood and predict prior intellectual ability with greater accuracy than socioeconomic estimates. However, the childhood development of type 1 diabetes could theoretically interfere with neurodevelopment. Therefore, the use of the NART as a covariate in the present study may have underestimated the magnitude of detrimental cognitive effects in later life attributable to EOD.

The present study provides clues to the causality of the association between EOD and cognitive ability. Given that EOD influenced cognitive ability independently of retinopathy and diabetes duration, any differences are unlikely to represent cumulative glycemic exposure. Others have hypothesized that cognitive differences associated with EOD depend on early childhood severe hypoglycemia exposure (39), although prospective studies demonstrating an independent influence of EOD on cognitive ability (6,9) partly refute this hypothesis. The precise age at

which severe hypoglycemia exposure occurred could not be accurately delineated in the present study, as severe hypoglycemia exposure was retrospectively determined. Therefore, the present findings cannot exclude detrimental effects of severe hypoglycemia in early childhood on the acquisition of intellectual abilities. Present observations imply that the unfavorable intellectual effects of EOD may be independent of glycemic exposure, clinical microangiopathy, and diabetes duration (6). School attendance problems (13), behavioral difficulties (14), and abnormal myelination (40) are alternative explanations for the observed differences in intellectual ability. Relative insulin deficiency during childhood neurodevelopment should also be considered. Insulin receptors are expressed in brain areas involved in cognition (particularly the limbic system) and may influence cognition through neurotransmitter metabolism and synaptic plasticity (41). Relative deficiency of insulin action on these receptors as a result of childhood type 1 diabetes could have potential neurodevelopmental sequelae.

Brain structure and EOD

Structural brain abnormalities were more frequent in those with EOD. The comparatively higher frequency of mild ventricular atrophy (61 vs. 20%) and greater lateral ventricular volumes observed in the EOD group are consistent with the hypothesis that EOD could be detrimental to brain development. Ventricular atrophy occurs during normal brain aging, and the higher prevalence observed in the EOD group could reflect suboptimal brain development or, alternatively, an advanced state of brain aging relative to chronological age. Gray or white matter volume measurements were not made, so that the differences observed could represent volumetric changes in gray matter, white matter, or both. Consistent with the present neuropsychological findings, the structural brain associations of EOD were independent of microangiopathy and diabetes duration and appeared unrelated to preceding severe hypoglycemia within the present methodological limitations.

Intracranial volume is determined by genetic, sex, and environmental factors; >90% of intracranial volume and subregional brain volumes are inherited (42). Sex and intracranial volume were entered into the volumetric model to facilitate the detection of differences associated with diabetes onset age. It could be argued that taking the covariance of intracranial volume into account could mask potential differences caused by EOD, based on the premise that EOD could impair brain growth. However, as no correlation between diabetes onset age and intracranial volume was observed, covariance for intracranial volume appeared appropriate.

MRI scans were rated for two types of WMLs: leukoaraiosis (27) and SPWMLs. Leukoaraiosis rating scales differ in sensitivity (28), and evaluators of the type of leukoaraiosis observed in the present study did not identify consistent differences between the study groups. EOD did not consistently predict the presence of leukoaraiosis; a statistically higher frequency was observed using the Wahlund scale (21) but not with any other scale (19,23,26). This observation may have reflected differences in sensitivity and scoring criteria inherent in rating scales or a type 1 statistical error. However, if the difference in leukoaraiosis determined by the Wahlund method is considered significant, this may corroborate results from animal studies suggesting that hyperglycemia may interfere with myelination (40). However, the independence from glycemic surrogates (retinopathy and diabetes duration) mitigates against this interpretation. Hippocampal SPWMLs were observed more frequently in association with EOD, and the hippocampus appears vulnerable in diabetes, with mesial temporal lobe sclerosis reported more frequently in those who developed diabetes in early childhood (43). However, the higher frequency of hippocampal SPWMLs observed in EOD subjects should be cautiously interpreted, as the analysis was based on small case numbers. Therefore, the present findings cannot conclude with any degree of certainty that EOD is associated with white matter changes.

In conclusion, the findings of the present study indicate that subtle but definite differences in brain structure and modest differences in specific intellectual and information-processing abilities are common in adults who developed type 1 diabetes before their seventh birthday. The coexistence of neuroradiological and intellectual performance differences implies that EOD may adversely affect neurodevelopment. The pathogenesis of the differences observed remains uncertain. However, the coexistence of cognitive and neuroradiological differences supports the presence of an organic component to their etiology, but does not exclude a coexistent psychosocial etiology (6). The present observations suggest that the differences observed are unlikely to be caused by chronic hyperglycemia or the development of microangiopathy or be a manifestation of the duration of diabetes, although a contribution from early childhood exposure to severe hypoglycemia cannot be excluded. Prospective neurodevelopmental evaluation of children with type 1 diabetes is required to validate the present findings and further explore the pathogenesis of the detrimental effects conferred upon the central nervous system by EOD.

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