Central Nervous System Function in Youth With Type 1 Diabetes 12 Years After Disease Onset

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OBJECTIVE — In this study, we used neurocognitive assessment and neuroimaging to examine brain function in youth with type 1 diabetes studied prospectively from diagnosis.

RESEARCH DESIGN AND METHODS — We studied type 1 diabetic ($n = 106$) and control subjects ($n = 75$) with no significant group difference on IQ at baseline 12 years previously by using the Wechsler Abbreviated Scale of General Intelligence, magnetic resonance spectroscopy and imaging, and metabolic control data from diagnosis.

RESULTS — Type 1 diabetic subjects had lower verbal and full scale IQs than control subjects (both $P < 0.05$). Type 1 diabetic subjects had lower *N*-acetylaspartate in frontal lobes and basal ganglia and higher myoinositol and choline in frontal and temporal lobes and basal ganglia than control subjects (all $P < 0.05$). Type 1 diabetic subjects, relative to control subjects, had decreased gray matter in bilateral thalami and right parahippocampal gyrus and insular cortex. White matter was decreased in bilateral parahippocampi, left temporal lobe, and middle frontal area (all $P < 0.0005$ uncorrected). T2 in type 1 diabetic subjects was increased in left superior temporal gyrus and decreased in bilateral lentiform nuclei, caudate nuclei and thalami, and right insular area (all $P < 0.0005$ uncorrected). Early-onset disease predicted lower performance IQ, and hypoglycemia was associated with lower verbal IQ and volume reduction in thalamus; poor metabolic control predicted elevated myoinositol and decreased T2 in thalamus; and older age predicted volume loss and T2 change in basal ganglia.

CONCLUSIONS — This study documents brain effects 12 years after diagnosis in a type 1 diabetic sample whose IQ at diagnosis matched that of control subjects. Findings suggest several neuropathological processes including gliosis, demyelination, and altered osmolarity.

Diabetes Care 32:445–450, 2009

The central nervous system (CNS) is a major organ system affected in type 1 diabetes, as both cerebral glucose and insulin levels are frequently abnormal even when diabetes is well controlled (1). Intracellular calcium toxicity and excitotoxic cellular damage, triggered by the synaptic release of excessive glutamate, have been identified as two potentially important mechanisms that produce selective neuronal necrosis during severe hypoglycemia (1), but other metabolite changes may also be important. Hyperglycemia disrupts blood-brain barrier function and depresses cerebral blood flow acutely, whereas chronic hyperglycemia is associated with cerebrovascular disease and neuropathy (1). The impact on the CNS of osmotic changes associated with constantly fluctuating glucose levels is unclear. Neurotransmitter pathways may also be affected in diabetes, as insulin is involved in regulation of the amine neurotransmitters (1).

There is a growing body of literature documenting pathophysiological CNS changes and neurocognitive deficits in adults with type 1 diabetes (2–6) as sometimes, but not universally, linked to specific illness variables such as disease duration or history of severe hypoglycemia or chronic hyperglycemia. Cognitive difficulties have also been reported in children, with deficits most evident in those with early-onset (≤5 years old) disease (7,8). Neuroimaging studies of youth have been limited to date (9,10) and understanding of the impact of type 1 diabetes on neurodevelopment is still based largely on inferences drawn from neurocognitive studies and from adult neuroimaging reports. Controlled, longitudinal studies are particularly informative in documenting illness-related changes in the CNS. The Diabetes Control and Complications Trial (DCCT) (11) showed no deterioration in cognitive function in either conventionally or intensively treated patients over an 18-year period. However, this study did not enroll participants at diagnosis and recruitment was limited to those >13 years of age. Thus, the DCCT was unable to document any illness-related effects that may have occurred before recruitment—in particular, the impact of diabetes on a developing CNS. Children have high cerebral energy needs associated with brain growth and "neural pruning" and may be more sensitive than adults to glucose fluctuations (1,7). It is important to document the specific neuropathological correlates of type 1 diabetes in younger populations, as better understanding of the impact of childhood-onset disease on CNS development will facilitate evidence-based pediatric management regimens.

Previously, we identified neurocognitive deficits 6 years after disease onset in youth studied prospectively from diagnosis (12). The current study reevaluated this cohort 12 years after study inception.

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Received 9 September 2008 and accepted 27 November 2008.
Published ahead of print at http://care.diabetesjournals.org on 16 January 2009. DOI: 10.2337/dc08-1657.

RESEARCH DESIGN AND METHODS

— Consecutive patients admitted to the Royal Children's Hospital, Melbourne, with newly diagnosed type 1 diabetes between 1990 and 1992 (n = 133) together with healthy control subjects (n = 126), stratified for age and sex. A history of CNS disease or trauma was an exclusion criterion. Twelve years later, all participants who could be located (125 type 1 diabetic patients and 93 control subjects: 94 and 74%, respectively) using the study database, Royal Children's Hospital, Melbourne and adult diabetes clinics, private endocrinologists, and the Health Insurance Commission were invited to take part in the current study. Of those located, 106 type 1 diabetic and 75 control subjects agreed to participate (rates of 85 and 81%, respectively).

All participants underwent neurocognitive testing. Participants were consecutively invited to undergo neuroimaging until available funding was exhausted. Blood glucose levels (BGLs) of diabetic participants were determined before assessment by capillary sample to ensure that subjects had a reading >4 mmol/l. This study was approved by the Human Ethics Research Committee of the Victorian Government Department of Human Services.

Measures

Neurocognitive assessment. The Wechsler Abbreviated Scale of General Intelligence (13) is a standardized, brief measure of intelligence providing full scale (FSIQ), verbal (VIQ), and performance (PIQ) IQ scores (mean ± SD 100 ± 15).

Magnetic resonance spectroscopy and imaging. Imaging was carried out on a 3-T scanner (GE Healthcare, Milwaukee, WI).

Magnetic resonance spectroscopy. Bilateral single-voxel spectra were acquired using a standard PRESS sequence to provide a metabolite profile from three brain regions of interest (ROIs): basal ganglia and frontal and temporal lobes. The ROIs were positioned using T1-weighted scout images. Basal ganglia ROIs were positioned over the lentiform nuclei, temporal lobe ROIs were positioned to include hippocampus and mesial temporal structures, and frontal lobe ROIs were placed above the third ventricle sufficiently posterior to avoid interference from curvature of the skull. Acquisition parameters were TE/TR = 30/3000 ms. For frontal and temporal spectra, isotropic 2-cm voxels were used, and for basal ganglia voxel size was 2 × 2 × 1.5 cm. Data were analyzed using software packages, SAGE/IDL (GE Healthcare; WI/RSI, Boulder, CO) and LCModel (14), with a basis set of 15 metabolites acquired on the same spectrometer. Data were included in analyses if the Cramer-Rao lower bound was <30% as determined by LCModel. Results are presented in institutional units approximating millimoles per liter. In vivo proton magnetic resonance spectroscopy (MRS) of brain provides information on the tissue content of total *N*-acetylaspartate (NAA) (including *N*-acetylaspartylglutamate), creatine + creatine phosphate, myoinositol, trimethylamines or choline-containing metabolites (Cho), and glutamine + glutamate.

Magnetic resonance imaging: volumetry. A fast spoiled gradient-recalled echo at steady-state sequence was used (TR/TE/TI = 13.8/2.7/500 ms, voxel size 0.48 × 0.48 × 2 mm). For T2 relaxometry, a modified, optimized Carr-Purcell-Meiboom-Gill multiecho sequence (14) was used (eight echoes, TE = 28.9–231 ms, TR = 6.24 s, 24 slices, 5-mm slice thickness, in-plane voxel size 0.94 × 1.88 mm). The slice plane was perpendicular to the long axis of the hippocampus. T2 maps were generated by fitting to a mono-exponential model with the inclusion of a baseline that minimizes the contribution of long T2 components (mainly cerebrospinal fluid) to the fit. For analyses, images were warped to standard space in which they could be compared and smoothed (with a 10-mm kernel). All analyses were performed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/software/spm2). Separate gray matter and white matter volumetry analyses were performed using optimized voxel-based morphometry (VBM) (15). Voxel-wise T2 changes were assessed using the approach of voxel-based relaxometry (16).

Biomedical measures. Participants with diabetes diagnosed at age ≤5 years were classified as having early-onset disease. Participants reported any episodes from diagnosis of hypoglycemia associated with seizure/coma, and these were corroborated through scrutiny of medical records. The sample was dichotomized into those who reported no events and those with a history of ≥1 event. A1C measurements from diagnosis were obtained for each patient (range 9–57, median 37) from hospital and clinic databases. The percentage of total time from diagnosis that A1C was ≥9.0% was calculated to estimate overall metabolic control.

Statistical analyses

SPSS (version 14; SPSS, Chicago, IL) was used for statistical analyses of demographic, IQ, and MRS data.

IQ. Group differences were examined using ANCOVA, covarying for socioeconomic status (SES), $FSIQ_{baseline}$, and time between baseline and current assessment.

MRS. Mean bilateral metabolite concentrations in each ROI were used in analyses. Group differences were examined using ANCOVA with age as a covariate.

Magnetic resonance imaging. ANCOVA was used to examine group differences in volume and T2, covarying for age. Volume analyses also included total brain volume and sex as covariates.

Multiple linear regression was used to predict IQ from illness variables (age of disease onset, hypoglycemia, and metabolic control), SES, $FSIQ_{baseline}$, and time between baseline and current assessment. Age of disease onset was highly correlated with age; hence, age was used as a predictor for regression analyses of MRS/magnetic resonance imaging (MRI) data, together with hypoglycemia and metabolic control. MRI regression analyses were restricted to anatomical areas shown to differ in the initial type 1 diabetic and control comparisons.

RESULTS

— Sample characteristics of participants are presented in Table 1. Type 1 diabetic and control participants did not differ on $FSIQ_{baseline}$, age, sex ratio, SES, or psychiatric symptoms. Time between baseline and current assessment was shorter in type 1 diabetic subjects (95% CI 0.37–1.0 years). Type 1 diabetic and control participants who underwent neuroimaging did not differ significantly on age or sex ratio, and there were no differences between type 1 diabetic subjects who had neuroimaging and those who did not on age of disease onset, hypoglycemia, or metabolic control. Group mean scores ± SD on IQ and MRS and MRI variables are presented in Tables 2 and 3.

Group (type 1 diabetic and control participants) differences on IQ and MRS/MRI variables

IQ. Type 1 diabetic subjects had lower VIQ (P = 0.03) and FSIQ (P = 0.05) than control subjects.

Table 1—*Sample characteristics*

	Type 1 diabetes	Control	Mean difference (type 1 diabetes − control) Estimate	95% CI	*P*
Sample size (*n*)	106	75			
Age (years)	20.5 ± 4.3	21.0 ± 3.8	−0.50	−1.74 to 0.74	0.4
Female sex (%)	49	51	−1.6	−16.0 to 12.9	0.9
SES (1 = high, 7 = low)	4.3 ± 1.1	4.1 ± 1.1	0.25	−0.08 to 0.59	0.14
Mental health (YSR/YASR total *t* score)	48.7 ± 11.5	49.5 ± 11.0	−0.75	−4.17 to 2.66	0.7
$FSIQ_{baseline}$	108.0 ± 15.1	110.6 ± 12.2	−2.66	−6.83 to 1.52	0.2
Time between baseline assessment and12-year follow-up (years)	12.7 ± 1.1	12.0 ± 1.1	0.70	0.37 to 1.03	<0.001
Neuroimaging (*n*)	79	51			
Age (years)	20.3 ± 4.3	20.6 ± 3.6	−0.25	−1.69 to 1.18	0.7
Female sex	41	47	−6.6	−2.3 to 10.5	0.5
BGL at imaging (mmol/l)	12.6 ± 5.4				
BGL at neurocognitive testing (mmol/l)	11.7 ± 5.9				
Most recent A1C (%)	9.2 ± 1.8				
Age at type 1 diabetes onset (years)	7.1 ± 3.7				
Early disease onset (%)	38				
≥1 episode severe hypoglycemia (%)	44				
Mean time A1C >9.0% (%)	41.95 ± 26.31				

Data are means ± SD unless otherwise noted. YASR, Young Adult Self Report; YSR, Youth Self Report.

MRS. The largest mean differences were in myoinositol and NAA, with myoinositol higher and NAA lower in type 1 diabetic participants. Smaller statistically significant mean differences (type 1 diabetic participants higher) were found in Cho in all locations.

MRI. Type 1 diabetic subjects, relative to control subjects, had decreased gray matter volume in bilateral thalami, right parahippocampal gyrus, and right insular cortex (supplemental Figure A1, available in online appendix at http://dx.doi.org/10.2337/dc08-57). Mean white matter volume was decreased in bilateral mesial temporal lobes (parahippocampal region), in other areas of the left temporal lobe, and in the left-middle frontal area. T2 relaxation times in type 1 diabetic participants were increased in the left superior temporal gyrus and decreased in bilateral lentiform nuclei, caudate nuclei and thalami, and the right insular area (all $P < 0.0005$ uncorrected).

Table 2—*Group (type 1 diabetic and control participants) differences on IQ and metabolites*

Outcome variable	Means Type 1 diabetes	Means Control	Mean difference* Estimate	95% CI	*P*
IQ					
VIQ	96.2	100.4	−3.64	−6.97 to −0.30	0.03
PIQ	106.4	109.1	−2.02	−5.46 to 1.43	0.25
FSIQ	101.3	105.1	−3.03	−6.07 to 0.00	0.05
Metabolite					
mI basal ganglia	3.46	3.17	0.29	0.11 to 0.48	0.002
mI frontal lobe	4.17	3.52	0.65	0.46 to 0.84	<0.001
mI temporal lobe	4.39	3.91	0.48	0.22 to 0.75	<0.001
Cr basal ganglia	6.88	6.96	−0.08	−0.32 to 0.16	0.5
Cr frontal lobe	5.39	5.37	0.01	−0.12 to 0.15	0.9
Cr temporal lobe	5.31	5.32	−0.02	−0.29 to 0.26	>0.9
Glx basal ganglia	11.50	11.37	0.14	−0.35 to 0.63	0.6
Glx frontal lobe	9.99	9.76	0.16	−0.26 to 0.58	0.4
Glx temporal lobe	8.43	8.31	0.12	−0.37 to 0.61	0.6
Cho basal ganglia	1.63	1.56	0.07	0.01 to 0.14	0.027
Cho frontal lobe	1.61	1.48	0.13	0.07 to 0.19	<0.001
Cho temporal lobe	1.72	1.64	0.09†	−0.00 to 0.18†	0.04†
NAA basal ganglia	7.98	8.47	−0.49	−0.83 to −0.15	0.005
NAA frontal lobe	8.27	8.67	−0.41	−0.65 to −0.16	0.001
NAA temporal lobe	7.50	7.84	−0.35	−0.72 to 0.03	0.07

*Adjusted mean difference estimate (from ANCOVA model) is type 1 diabetes − control. †This analysis was based on nonparametric procedures because of an extreme value in the original data set; the estimate and approximate 95% CI are for a difference in the location of the populations. The *P* value is from the Mann-Whitney *U* test. Cr, creatine + creatine phosphate; Glx, glutamine + glutamate; mI, myoinositol.

Illness-related predictors of CNS outcome in type 1 diabetic participants

Regression analyses of illness-related predictors of IQ, MRS, and MRI findings are presented in supplemental Table A1, available in an online appendix.

IQ. In each regression, SES and $FSIQ_{baseline}$ contributed significantly to the model. In addition, hypoglycemia predicted lower VIQ (R^2 change = 0.032, $P = 0.01$) and early disease onset predicted lower PIQ (R^2 change = 0.135, $P < 0.001$) and FSIQ (R^2 change = 0.064, $P < 0.001$). The verbal IQ of the hypoglycemia subgroup was nearly ⅓ SD below that for type 1 diabetic patients with no hypoglycemia (adjusted mean ± SEM 93.8 ± 1.3 vs. 98.2 ± 1.1). Early-onset participants

Table 3—*Group (type 1 diabetic and control) differences on grey matter volume, white matter volume, and T2 relaxation time*

Outcome variable	Cluster*	Means†		Mean difference‡		
		Type 1 diabetic	Control	Estimate	99.9% CI‖	*t*§
GM volume decrease						
Left thalamus	1,718	0.531	0.568	0.038	0.005 to 0.071	3.93
Right thalamus	1,623	0.525	0.563	0.038	0.005 to 0.071	3.93
Left frontal precentral/insular gyrus	373	0.532	0.575	0.051	0.003 to 0.098	3.55
Right superior frontal gyrus	287	0.431	0.478	0.049	0.003 to 0.095	3.58
Right frontal precentral gyrus	78	0.349	0.390	0.046	0.003 to 0.088	3.60
Right parietal postcentral gyrus	104	0.375	0.417	0.046	0.002 to 0.089	3.51
Right parahippocampal gyrus	79	0.513	0.554	0.046	0.001 to 0.091	3.45
WM volume decrease						
Right parahippocampal WM	183	0.275	0.329	0.050	0.006 to 0.094	3.82
Left parahippocampal WM	290	0.231	0.275	0.042	0.002 to 0.082	3.55
Left-middle frontal WM	207	0.149	0.201	0.049	0.007 to 0.090	3.94
Left temporal WM	156	0.092	0.131	0.037	0.003 to 0.071	3.69
Left insular WM	158	0.182	0.230	0.043	0.004 to 0.082	3.69
Left-middle temporal WM	126	0.386	0.458	0.074	0.006 to 0.142	3.56
T2 decrease						
Left lentiform nucleus	299	625.5	638.0	14.3	1.0 to 27.6	3.63
Right lentiform nucleus	1,058	645.4	662.9	19.1	3.1 to 35.1	4.01
Left caudate nucleus	1,843	614.0	627.7	15.4	2.2 to 28.6	3.92
Right caudate nucleus	2,901	644.7	659.3	16.2	2.2 to 30.3	3.88
Left thalamus	496	678.8	693.2	15.5	1.78 to 29.2	3.81
Right thalamus	753	653.7	669.8	17.6	2.6 to 32.63	3.95
Red nuclei (bilaterally)	225	664.1	676.4	13.7	1.0 to 26.4	3.63
Right frontal WM	251	706.1	727.7	22.8	1.4 to 44.18	3.59
Right insular/superior temporal gyrus	146	712.0	736.0	26.0	1.2 to 50.9	3.53
Corpus callosum	24	706.9	722.0	15.7	0.7 to 30.7	3.52
Right parietal WM	23	716.6	732.4	16.3	0.3 to 32.3	3.44
T2 increase						
Left-middle temporal GM	37	793.8	762.1	−30.0	−59.6 to −0.5	−3.43

Magnetic resonance regions are indicated as abnormal by voxel-based analysis (type 1 diabetic versus control participants using a one-tailed *t* test at $P = 0.0005$, noncorrected). *The cluster size is the number of voxels in a contiguous volume of suprathreshold voxels. †Mean values of voxel-based data are not adjusted for covariates. T2 values are in milliseconds; volume changes are in liters. ‡The mean difference is adjusted for covariates. §Since significance is the selection criteria for these areas, the *t* statistic is reported. ‖The bidirectional CIs are shown at 99.9% (equivalent threshold to the two one-tailed *t* tests at $P = 0.0005$). GM, gray matter; WM, white matter.

had a PIQ more than 1/2 SD and an FSIQ 1/3 SD below that for those with later-onset type 1 diabetes (101.6 ± 2.5 vs. 109.2 ± 1.7 and 97.8 ± 2.1 vs. 103.4 ± 1.4, respectively).

MRS. Poor metabolic control predicted higher levels of myoinositol in basal ganglia (R^2 change = 0.055, $P = 0.04$), and older age predicted lower levels of glutamine + glutamate in frontal lobes (R^2 change = 0.116, $P < 0.01$) and NAA in temporal lobes (R^2 change = 0.133, $P < 0.01$).

MRI. Regression analyses of MRI data in areas implicated in the previous group comparisons revealed the dominating influence of age in explaining variation in volume and T2: R^2 change = 0.247, $P < 0.001$ (gray matter volume lentiform); R^2 change = 0.060, $P < 0.02$ (gray matter volume thalamus); R^2 change = 0.578, $P < 0.001$ (T2 lentiform); and R^2 change = 0.418, $P < 0.001$ (T2 thalamus). Hypoglycemia predicted reduced gray matter volume in the thalamus (R^2 change = 0.045, $P < 0.03$), and poor metabolic control was associated with decreased T2 in the thalamus (R^2 change = 0.021, $P < 0.05$).

In view of the strong association between older age and volume and T2 reduction in type 1 diabetic subjects, we investigated how group and age predicted each of the MRI variables. The models included an interaction term of group by age, which was statistically significant in all analyses. For volume, the models predicted small positive changes with age for control subjects and relatively larger negative changes for type 1 diabetic subjects (lentiform, $P_{interaction} = 0.002$, age slopes: type 1 diabetic subjects −0.0038, control subjects 0.0001; thalamus, $P_{interaction} = 0.046$, age slopes: type 1 diabetic subjects −0.0025, control subjects 0.0012). For T2, the models predicted relatively larger negative changes for type 1 diabetic subjects than for control subjects (lentiform, $P_{interaction} = 0.013$, age slopes: type 1 diabetic subjects −5.11, control subjects −3.17; thalamus, $P_{interaction} = 0.017$, age slopes: type 1 diabetic subjects = −5.25, control subjects = −2.85).

BGL at time of testing. Correlations between BGL before neuropsychological assessment and IQ scores and between BGL before scanning and metabolite profiles were calculated and ranged from $r = 0.001$ to $r = -0.242$ (all $P > 0.05$). To further examine the possible confounding of intercurrent hyperglycemia on study findings, data from type 1 diabetic participants with BGLs >15 mmol/l at the time

of testing ($n = 34$) were removed and the data were reanalyzed. Group differences on VIQ and FSIQ became trends only ($P < 0.06$ and $P < 0.07$, respectively). The significance of the group difference on basal ganglia NAA was also reduced ($P < 0.08$) after removal of type 1 diabetic participants with BGL >15 ($n = 19$) at the time of scanning. All other group differences and illness-related predictors of IQ and metabolites were unchanged.

CONCLUSIONS — This study is the first to document CNS effects 12 years after diagnosis in youth with type 1 diabetes whose neurocognitive profile at disease onset was not different from that of control subjects. Metabolites and IQ results were largely unchanged after removal of data from type 1 diabetic participants with high BGLs at the time of assessment, suggesting that study findings reflect stable changes in CNS function. Group differences on IQ were marginal and appear to reflect the selective impact of specific illness risk factors. Lower VIQ was associated with a positive history of hypoglycemia, whereas early-onset disease predicted lower PIQ and FSIQ. The association between early-onset disease and lower IQ, particularly PIQ, is a consistent finding (7,8). Hypoglycemia-related effects on VIQ have also been reported previously in the pediatric literature (8,12) but were not found in the DCCT (11), suggesting that the developing CNS may be especially vulnerable to hypoglycemia. It is important to note that illness-related effects on IQ, although statistically significant, are small, and individuals with type 1 diabetes function well within the average range. However, even mild decrements in ability may have functional significance during childhood when new knowledge is being acquired. Of participants who had reached school-leaving age at follow-up (type 1 diabetic subjects, $n = 76$; control subjects, $n = 55$), 17% fewer type 1 diabetic subjects than control subjects (68 vs. 85%, $P < 0.01$) completed year 12, the pretertiary year of education in Australia.

This study showed lower mean NAA and higher mean myoinositol and Cho in type 1 diabetic subjects than in control subjects. The magnitudes of these differences were in the range of 10–15% and are similar to those reported for diseases such as dementia, epilepsy, and Parkinson's disease (17,18). There are also similarities between current findings and previous reports in diabetes (4,5,10), although direct comparison is difficult because methodology has varied, with different brain regions assessed and some samples including both type 1 and type 2 diabetic participants. With one exception (10), study populations have been older than the current sample. NAA is a marker of neuronal density or viability, with lower levels indicative of neuronal death and/or decreased neuronal metabolism (17). Lower mean NAA is consistent with animal models of diabetes suggesting that chronic hyperglycemia reduces neuronal number and impedes myelination (19). Although we were not able to relate NAA directly to metabolic control in the current study, NAA levels correlated inversely with lifetime glycemic exposure in another report (5).

Myoinositol is a marker of changes in osmolarity, and increased levels are associated with both gliosis and demyelination (17). In the current study, poorer metabolic control was associated with higher levels of myoinositol in basal ganglia which, together with other reports of elevated myoinositol in patients recovering from diabetic ketoacidosis (20), suggests that higher levels may represent a homeostatic response of the brain to prolonged hyperglycemia. Cho levels are increased with demyelination and other forms of cell membrane breakdown, including gliosis (17). In diabetes, increases in both myoinositol and Cho are consistent with glial proliferation due to tissue hypoxia in the context of chronically elevated blood glucose levels (21). As with a previous report (10), metabolite profiles were not related to history of hypoglycemia.

Volumetric measurements can identify regionally specific macroscopic atrophy associated with neuronal degeneration. Musen et al. (2), using VBM, reported reduced gray matter densities in temporal brain regions and left thalamus. Our finding of decreased mean gray matter in thalamus is similar, but, in addition, we found reduced mean gray matter volume in insular cortex and frontal precentral regions and a reduction in mean white matter volume in mesial temporal areas. Previous reports have linked VBM changes to a previous history of either chronic hyperglycemia (2,3,8) and/or severe hypoglycemia (2,8). In the current study, hypoglycemia was associated with volume reduction in the thalamus, poor control predicted decreased T2 in the thalamus, and there were strong associations between older age and reduced volume and T2 in anterior and temporal brain regions as well as thalamus, caudate, and lentiform nuclei.

The volume group differences found in this study reach levels of ~10%, comparable to changes in temporal lobe epilepsy in which volume reduction is ~10–15% (22). T2 group differences of 3% in the current study are smaller than those of 5–20% reported in other CNS diseases (23) and may in part reflect an osmotic influence of acutely elevated glucose on tissue water distribution as well as or instead of any longer-term impact of the illness. In the current study, older age was the strongest predictor of volume and T2 decrease in type 1 diabetic subjects. Older age is a surrogate for later disease onset in this cohort, as duration of illness was controlled; hence, these findings are counterintuitive, given the consistent association between early disease onset and neurocognitive deficits reported previously (7,8,11). It is now recognized, though, that CNS maturation continues into the third decade of life (24), and it is possible that findings reflect an interaction between type 1 diabetes and the final stages of neurodevelopment, with the early-onset subgroup yet to experience this disruption. The suggestion by Biessels et al. (25) that diabetes is a model for "accelerated [CNS] aging" provides an alternative explanation for our findings. That is, rather than reflecting disrupted neurodevelopment, the greater volume loss in our older and later-onset participants may represent the earliest stages of cerebral microvascular disease or some other neurodegenerative process.

The current findings are suggestive of a number of possible illness-related neuropathological processes, including gliosis, demyelination, and changes in osmolarity and neural cell type/viability. Anterior and temporal brain regions have particularly high glucose demands and increased sensitivity to glucose disruption (1); thus, it not surprising that these brain regions show reduced brain volumes, altered T2 relaxation times, and metabolite changes. Relationships between specific illness variables and CNS effects are more difficult to disentangle. There were strong associations between age and IQ and structural brain changes but in the opposite direction. Early-onset diabetes (and younger age) was associated with lower PIQ and FSIQ, whereas older age predicted lower levels of NAA, reduced brain volumes, and altered T2. Metabolite profiles are more suggestive of hyperglycemia than of hypoglycemia-mediated neuro-

toxicity in the developing CNS. It is possible that specific illness variables exert different effects on the CNS, but inconsistent associations may also reflect difficulties in obtaining reliable and comprehensive metabolic control histories, including documentation of diabetes complications. Further studies, involving large multicenter cohorts, meticulous collection of metabolic control histories, documentation of diabetes complications, and tight control over the glycemic level of participants at the time of assessment, are needed to fully understand the pathogenesis of CNS changes in childhood-onset diabetes.

Acknowledgments— This research was supported by Juvenile Diabetes Foundation International (grant 1-2003-135). E.A.N. and F.J.C. received the Australian Diabetes Society-Servier National Action Plan grant, the *beyondblue* Victorian Centre of Excellence in Depression grant, and National Health and Medical Research Council Project Grant 334354. E.A.N. also received grant support from Australian Rotary Health Research Fund.

E.A.N. received lecture fees from Novo Nordisk and research grant support from Eli Lilly. G.A.W. received consulting fees from IPSEN, has equity in Antisense Therapeutics Limited (Australia) and Neuren (Australia), and is currently receiving research support from Novo Nordisk and Sandoz. F.J.C. received lecture fees and/or consultancy fees from Novo Nordisk, Eli Lilly, and Medtronic and research grants from Eli Lilly and Medtronic. No other potential conflicts of interest relevant to this article were reported.

We acknowledge the contributions of Deb Boyce, SN, in locating and recruiting participants and Professor Graeme Jackson of the Brain Research Institute, Austin Health, for his support for the project.

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