Impact of Early Diabetic Ketoacidosis on the Developing Brain

Diabetes Care 2019;42:443–449 | https://doi.org/10.2337/dc18-1405

*Tandy Aye,[1] Paul K. Mazaika,[2] Nelly Mauras,[3] Matthew J. Marzelli,[2] Hanyang Shen,[2] Tamara Hershey,[4] Allison Cato,[5] Stuart A. Weinzimer,[6] Neil H. White,[7] Eva Tsalikian,[8] Booil Jo,[2] and Allan L. Reiss,[2,9] for the Diabetes Research in Children Network (DirecNet) Study Group**

OBJECTIVE

This study examined whether a history of diabetic ketoacidosis (DKA) is associated with changes in longitudinal cognitive and brain development in young children with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Cognitive and brain imaging data were analyzed from 144 children with type 1 diabetes, ages 4 to <10 years, who participated in an observational study of the Diabetes Research in Children Network (DirecNet). Participants were grouped according to history of DKA severity (none/mild or moderate/severe). Each participant had unsedated MRI scans and cognitive testing at baseline and 18 months.

RESULTS

In 48 of 51 subjects, the DKA event occurred at the time of onset, at an average of 2.9 years before study entry. The moderate/severe DKA group gained more total and regional white and gray matter volume over the observed 18 months compared with the none/mild group. When matched by age at time of enrollment and average HbA_{1c} during the 18-month interval, participants who had a history of moderate/severe DKA compared with none/mild DKA were observed to have significantly lower Full Scale Intelligence Quotient scores and cognitive performance on the Detectability and Commission subtests of the Conners' Continuous Performance Test II and the Dot Locations subtest of the Children's Memory Scale.

CONCLUSIONS

A single episode of moderate/severe DKA in young children at diagnosis is associated with lower cognitive scores and altered brain growth. Further studies are needed to assess whether earlier diagnosis of type 1 diabetes and prevention of DKA may reduce the long-term effect of ketoacidosis on the developing brain.

Diabetic ketoacidosis (DKA) is the most common acute cause of morbidity and mortality in youth with type 1 diabetes. An episode of DKA (1,2) has acute structural effects on the brain, such as clinical and subclinical cerebral edema (3), at the time of diagnosis as well as MRI-associated volume and diffusion tensor imaging (DTI) changes 3 months after diagnosis (4). A history of DKA has been associated with long-term adverse cognitive effects (4–8). Subtle learning and emotional problems and poor concentration have been reported by parents and providers in children after an episode of DKA, and evidence suggests long-lasting decreases in memory function in school-aged children (ages 7–16 years) years after a DKA episode (5).

[1]Division of Pediatric Endocrinology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA
[2]Center for Interdisciplinary Brain Sciences Research, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA
[3]Division of Pediatric Endocrinology, Department of Pediatrics, Nemours Children's Health System, Jacksonville, FL
[4]Departments of Psychiatry and Radiology, Washington University School of Medicine, St. Louis, MO
[5]Division of Neurology, Department of Pediatrics, Nemours Children's Health System, Jacksonville, FL
[6]Section of Pediatric Endocrinology, Department of Pediatrics, Yale University, New Haven, CT
[7]Division of Endocrinology and Diabetes, Department of Pediatrics, Washington University School of Medicine, St. Louis, MO
[8]Division of Endocrinology and Diabetes, Stead Family Department of Pediatrics, University of Iowa, Iowa City, IA
[9]Departments of Radiology and Pediatrics, Stanford University School of Medicine, Stanford, CA

Corresponding author: Tandy Aye, taye@stanford.edu

Received 2 July 2018 and accepted 19 November 2018

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-1405/-/DC1.

**A complete list of the members of the Diabetes Research in Children Network (DirecNet) Study Group can be found in the Supplementary Data.*

However, few studies have examined the effects of a DKA episode on cognitive and brain development from a longitudinal perspective, especially in young children with type 1 diabetes (9). The goal of this study was to determine how the severity of a DKA episode is associated with longitudinal memory and brain changes in young children (4–10 years) with type 1 diabetes.

RESEARCH DESIGN AND METHODS

We analyzed data from 144 children with type 1 diabetes, ages 4.0 to <10.0 years, who participated in the Diabetes Research in Children Network (DirecNet) study across five clinical centers (Nemours Children's Clinic in Jacksonville, Stanford University, University of Iowa, Washington University in St. Louis, and Yale University). All procedures were approved by the local institutional review boards and a National Institutes of Health–designated Data Safety Monitoring Board. Parents or legal guardians signed informed consents, and children older than 7 years of age provided assent, according to local guidelines.

All participants were screened for medical history to exclude for neurologic disorders, learning disabilities, psychiatric conditions, prematurity (<34 weeks' gestation), low birth weight (<2,000 g) and contraindications for MRI. Diabetes history, lifetime hyperglycemic index calculation, age-appropriate battery of cognitive testing, and unsedated MRI scans were completed as previously described (6,10–13).

Briefly, MRI scans were performed on Siemens 3T Tim Trio systems using a standard 12-channel head coil. Sagittal T1 images were acquired using a magnetization-prepared rapid gradient echo sequence: repetition time = 2,300 ms, echo time = 2.98 ms, inversion time = 900 ms, flip angle = 9°, slice thickness = 1 mm, field of view = 25.6 cm × 24 cm, 160 slices, matrix = 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm, and duration = 4:54 min. Diffusion-weighted echo planar scans were acquired in 30 directions with repetition time = 8,000 ms, echo time = 99 ms, b-value = 1,000 s/mm^2, 64 axial slices, voxel size = 2.0 × 2.0 × 2.0 mm, and duration = 4:59 min.

The cognitive battery covered intelligence quotient (IQ), executive function, learning and memory, and processing speed using age-appropriate measures. In addition, the Conners' Continuous Performance Test II (CPT2), an assessment of various facets of attention, was administered. During the CPT2, participants are instructed to respond to all letters presented consecutively on a computer screen with a button press, except for a specific target letter ("X"), to which they are instructed to withhold (i.e., inhibit) their response (14).

Blood glucose values were checked hourly and were required to be between 70 and 300 mg/dL during cognitive testing as well as before and after MRI scans. All participants underwent a baseline physical and neurologic exam.

DKA severity was modeled using an ordinal scale: none, mild, moderate, and severe. Family reports of DKA were confirmed with laboratory values in the medical records. The biochemical criteria for the diagnosis of DKA include hyperglycemia (blood glucose >200 mg/dL), with a venous pH <7.3 and/or bicarbonate <15 mmol/L. Severity of the acidosis varies from mild (venous pH 7.21–7.3, bicarbonate 11–15 mmol/L), to moderate (pH 7.11–7.2, bicarbonate 5–10 mmol/L), to severe (pH <7.1, bicarbonate <5 mmol/L) (15). Participants with diabetes were divided into two DKA subgroups according to the severity of the past DKA event. These subgroups consisted of individuals with none (n = 86) or mild (n = 12) past events and those with moderate (n = 18) or severe (n = 12) events. None and mild were placed together because participants with mild DKA are often treated as outpatients under the care of their provider, are not admitted to a hospital, and do not receive insulin drip infusion as part of their treatment plan.

To examine the specific effect of DKA severity, additional post hoc analyses were performed after matching a subgroup of 30 participants who experienced the episode of none/mild DKA to the 30 participants who experienced the moderate/severe episode of DKA by age at enrollment and glycemic exposure. During the 18-month interval, there were four episodes of DKA (two mild and two moderate) in four subjects. These subjects were excluded from the analysis to avoid the confounding of DKA effects occurring during the follow-up period in a small number of participants.

Glycemic Parameters

We investigated correlations of DKA severity with onset age, duration, and indices of glycemic exposure as previously reported (6,10–12). The participants wore a blinded continuous glucose monitor (CGM) for 10 days quarterly, close to the time of the HbA_{1c} measurement, to estimate their blood glucose characteristics (11,12). Glycemic exposures during the 18-month longitudinal study (average HbA_{1c}) were estimated by *1*) averaging the HbA_{1c} measurements collected quarterly, *2*) calculating the average fraction of time for CGM values >300 mg/dL, and *3*) calculating the mean amplitude of glycemic excursion (MAGE).

Brain Structural Analysis

Voxel-based morphometry (VBM) analysis was performed using parametric methods as previously described (11,12) as well as nonparametric methods. Briefly, images were segmented into gray and white matter volumes using established VBM methods, and regional differences in brain growth between groups were analyzed in MATLAB. Parametric analyses were performed using the VBM toolbox (C. Gaser, University of Jena, Jena, Germany; http://dbm.neuro.uni-jena.de/vbm/), and nonparametric analyses were performed using the Statistical nonParametric Mapping (SnPM) toolbox (T. Nichols et al., University of Warwick, Coventry, U.K.; http://warwick.ac.uk/snpm). For DTI, images were inspected for artifacts using DTI Studio (www.mristudio.org). Usable scans were processed with tract-based spatial statistics for longitudinal studies (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) to generate whole-brain maps of fractional anisotropy, axial diffusion, and radial diffusion, which were transformed onto a template image. Statistical analyses were performed using threshold-free cluster enhancement and permutation analyses (5,000 iterations) from the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl/). Growth was measured as a difference in image volume, fractional anisotropy, axial diffusion, or radial diffusion between the baseline and 18-month assessments. All data were covaried for age at baseline and sex, and regional VBM data were also covaried for total gray (or white) matter volume at baseline.

Cognitive Score Analysis

The neurocognitive testing methods have been previously described in detail (6,10). Longitudinal mixed-effects modeling was used in modeling repeated cognitive outcomes to improve power and allow for more optimal handling of missing data. Specifically, a random intercept model assuming a linear trend between the baseline (T_b) and 18 months (T_{18}) was used with maximum likelihood estimation implemented in R package lme4 (16). In the mixed-effects analyses, the change (slope) in the outcome is modeled as the key dependent variable predicted by the DKA status (none/mild vs. moderate/severe). All mixed-effects analyses were conducted conditional on baseline age.

RESULTS

Demographics

No participant experienced more than one episode of DKA, and all but four participants experienced their DKA episode at diagnosis. The moderate/severe DKA group was significantly younger ($P < 0.02$), had an earlier age of onset ($P < 0.01$), and had a higher average HbA_{1c} over the 18-month interval between assessments ($P < 0.03$) (Table 1). The parental education and family income levels were similar between groups. When the subgroups were matched for age and HbA_{1c} exposure, there were no significant demographic or glycemic differences at baseline or at 18 months. The CGM data showed that those in the moderate/severe group spent more time in the >300 mg/dL range compared with the none/mild group. The duration of type 1 diabetes was not significantly different between the two groups. The median time from the DKA event to the first brain structural and cognitive evaluation was 2.9 years and was not significantly different between the two groups. No gross neurologic signs or symptoms were identified in any of the participants.

Growth of Total Brain Volume

Anatomical and diffusion-weighted images were acquired, processed, and analyzed from 128 subjects (imaging data for 9 subjects were unusable because of motion artifacts) (Table 1). Data for neurocognitive testing were available for 137 subjects. The moderate/severe DKA group had greater growth of total white matter volume (WMV) than the none/mild group ($P < 0.04$) during the 18-month study interval, but there were no differences for total gray matter volume (GMV) growth between the groups ($P = 0.14$) (Table 1). When the subgroups were matched for age and HbA_{1c} exposure, the moderate/severe group had greater growth than the none/mild group for total WMV ($P < 0.04$) and total GMV ($P < 0.04$). The estimated mean growth rates were 33% higher for GMV and 32% higher for WMV for the moderate/severe group (Table 1). There were no significant cross-sectional differences in total volume at either time point, although the estimated volumes were slightly smaller for the moderate/severe group. Thus, both total GMV and WMV of the moderate/severe group were approaching values observed in the none/mild group during the study interval.

Growth of Regional Brain Volumes

Regional VBM results are summarized in Table 2. Results from the parametric analysis showed the moderate/severe

Table 1—Characteristics of study subjects

	Unmatched			Matched for HbA_{1c} and age		
	None/mild	Moderate/severe		None/mild	Moderate/severe	
	n = 98	*n* = 30	*P* values	*n* = 30	*n* = 30	*P* values
Demographics						
Sex						0.07
Male	55	11		18	11	
Female	43	19		12	19	
Age at baseline (years)	7.18 (1.7)	6.35 (1.4)	0.02	6.38 (1.5)	6.35 (1.4)	0.94
Onset age (years)	4.37 (1.8)	3.36 (2.0)	0.01	3.74 (1.5)	3.36 (2.0)	0.41
Diabetes duration at T_b	2.73 (1.9)	2.94 (1.9)	0.45	2.56 (1.9)	2.94 (1.9)	0.45
Glycemic characteristics						
Avg HbA_{1c} (%) over 18 months	7.8 (0.8)	8.2 (0.9)	0.02	7.9 (0.8)	8.2 (0.9)	0.19
Avg HbA_{1c} (mmol/mol) over 18 months	62 (9)	66 (10)		63 (9)	66 (10)	
Avg AOC 70 mg/dL (%)	0.7 (0.5)	0.8 (0.6)	0.48	0.7 (0.6)	0.8 (0.7)	0.67
Avg AOC >300 mg/dL (%)	12.8 (7.4)	17.3(8.7)	0.01	12.6 (6.9)	17.3 (8.7)	0.02
MAGE (mg/dL)	157 (24)	175 (26)	0.11	161 (27)	175 (26)	0.52
Brain volume						
GMV_T_b (mL)	694 (54)	672 (48)	0.55*	688 (51)	672 (48)	0.52*
WMV_T_b (mL)	449 (41)	433 (32)	0.97*	438 (41)	433 (32)	0.73*
GMV_T_{18} (mL)	703 (54)	685 (49)	0.76*	698 (48)	685 (49)	0.70*
WMV_T_{18} (mL)	459 (42)	448 (34)	0.66*	449 (41)	448 (34)	0.49*
Brain growth during study						
GMV growth rate (mL/year)	5.7 (5)	8.5 (5)	0.14*	6.4 (5)	8.5 (5)	0.04*
WMV growth rate (mL/year)	7.2 (4)	9.5 (4)	0.04*	7.2 (4)	9.5 (4)	0.04*

Data are presented as *n* or mean (SD). For the unmatched groups, the moderate/severe group was significantly younger in age, younger at onset age, and had higher glycemic exposure during the study. The matched subgroups reduced those differences. For the CGM data, Avg AOC (area over the blood concentration–time curve) 70 mg/dL is the average amount of time spent under 70 mg/dL, Avg >300 mg/dL is the average time spent over 300 mg/dL. For the brain volume data, growth rate is calculated as the difference in $T_{18} - T_b$ divided by time interval in years. *Covaried for age and sex.

Table 2—Differences in regional brain growth dependent on DKA severity

Brain matter	Regions contained in cluster	Volume (mL)	*P* value*
GMV	Bilateral postcentral/angular/supramarginal gyri, inferior parietal lobule, bilateral cuneus, precuneus, left middle temporal gyrus	68.1	<0.001
GMV	Left frontal lobe (superior/middle/inferior frontal gyri and precentral gyrus)	33.3	0.001
GMV	Left bilateral cingulate (anterior/middle)	26.5	0.002
WMV	Left frontal lobe (SFG, MFG, precentral gyrus), left temporal lobe (STG, MTG), left parietal lobe (postcentral/angular/supramarginal gyri, IPL), left occipital lobe (precuneus), as well as cingulum (anterior, middle), corpus callosum, and near left thalamus, left hippocampus, and left caudate	95.4	<0.001

Regions where there is greater growth in those who experienced moderate/severe DKA compared with the none/mild group. IPL, inferior parietal lobe; MTG, middle temporal gyrus; SFG, superior frontal gyrus; STG, superior temporal gyrus. *Statistically significant ($P < 0.05$).

group had increased GMV growth in parietal, occipital, frontal, and cingulate regions relative to the none/mild group after adjusting for total GMV ($P < 0.001$ to $P = 0.002$; see Fig. 1). When the subgroups were matched for age and HbA_{1c} exposure, results were largely similar (see Supplementary Fig. 1), with additional between-group differences found in temporal and insular regions ($P < 0.001$). Nonparametric analysis showed consistent—although less extensive—results for the unmatched ($P = 0.033$) and matched groups ($P = 0.006$).

For WMV, parametric analysis showed increased growth in the moderate/severe group relative to the none/mild group in many brain regions, including parietal, occipital, frontal, temporal, and cingulate regions ($P < 0.001$). The matched subgroup analysis yielded similar results (see Supplementary Table 1) with additional frontal, parietal, and occipital regions. Nonparametric analysis showed consistent although less extensive results for the unmatched ($P = 0.02$) and matched groups ($P = 0.004$).

DTI

Comparisons for none/mild versus moderate/severe did not show any significant clusters for the DTI analysis at baseline or at 18 months and did not show significant between-group differences in trajectory over the 18-month course of the study.

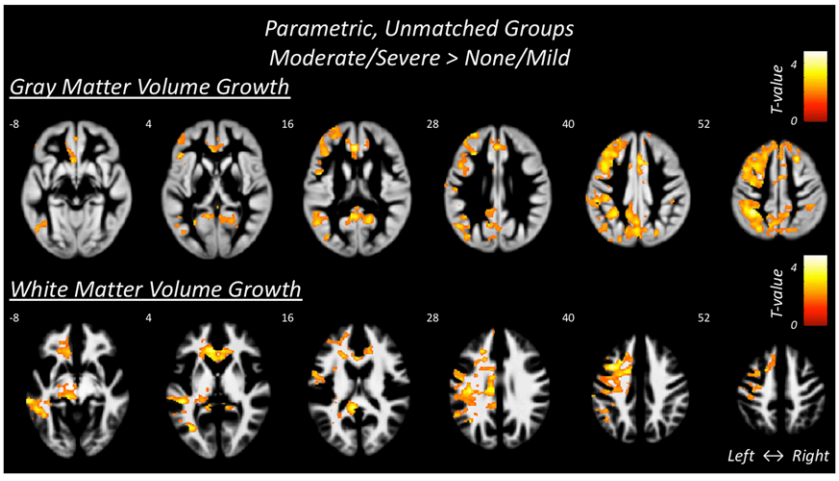

Figure 1—VBM regions of increased volume growth. Gray and white matter regions where participants with a history of moderate/severe DKA compared with those who experienced none/mild DKA had more growth ($T_{18} - T_b$) in GMV and WMV. Color map represents the statistical significance of growth differences between groups.

Cognitive Performance

The median time from the DKA event to cognitive testing was 2.9 years (range 0.1–7.6) at baseline and 4.7 years (range 1.7–9.1) at 18 months. The estimated group differences in the key outcome measures based on longitudinal mixed-effects modeling and effect sizes are reported in Table 3. At baseline, children with the moderate/severe DKA episode history scored slightly lower in the Vocabulary subscale than children with the none/mild episode history ($P = 0.014$). At 18 months, children with the moderate/severe DKA episode history scored about 6 points lower in Full Scale IQ than children with the none/mild episode history ($P = 0.030$). CPT2 scores for the two groups were not significantly different at baseline; however, at 18 months, children with the moderate/severe DKA episode history showed significantly lower scores. In general, the two groups showed no significant differences in the Word List subscales. Children with the moderate/severe DKA episode history scored similarly at baseline but significantly lower at 18 months in immediate and delayed Dots Location subscales, resulting in a larger difference between baseline and 18 months for the delayed Dots Location subscale ($P = 0.021$). We repeated the same longitudinal analyses using the subsample matched based on age and HbA_{1c}, and the results were consistent with those from the full sample with somewhat more pronounced group differences (see Supplementary Table 2).

CONCLUSIONS

Multiple studies have reported cognitive differences in children with type 1 diabetes, particularly in those diagnosed before age 5 years (17,18); however, the mechanisms for these differences are unknown. Because the incidence of severe DKA is higher in children younger than 5 years (19) the severity of DKA at diagnosis may be a contributing factor. Few pediatric studies have examined the effect of DKA on the brain and cognitive performance (5,7,9,20), and these studies defined DKA as pH <7.3 or bicarbonate <15 mmol/L. To our knowledge, our study is the first to report that history of DKA, modulated by severity, results in longitudinal changes in brain imaging and cognitive outcomes in young children. Compared with the none/mild

Table 3—Differences in cognitive scores between none/mild and moderate/severe DKA groups based on longitudinal mixed-effects modeling

			Group effect at T_b			Group effect at T_{18}			Group effect at T_{18} vs. T_b (slope difference)		
	Battery	Subscale	Estimate	*P* value	Cohen *d**	Estimate	*P* value	Cohen *d**	Estimate	*P* value	Cohen *d**
IQ	WPPSI3/WASI	Full Scale IQ Child Standard Score	−3.990	0.136	−0.325	**−5.816**	**0.030**	**−0.473**	−1.826	0.342	−0.149
		Verbal IQ Child Standard Score	−5.545	0.050	−0.425	−3.837	0.182	−0.294	1.709	0.478	0.131
		Performance IQ Child Standard Score	−2.141	0.485	−0.150	−5.622	0.071	−0.395	−3.481	0.155	−0.245
		Vocabulary Child Scaled Score	**−1.384**	**0.014**	**−0.542**	−0.613	0.279	−0.240	0.771	0.150	0.302
		Block Design Child Scaled Score	−0.607	0.368	−0.188	−1.005	0.136	−0.311	−0.398	0.496	−0.123
		Similarities Child Scaled Score	−0.546	0.308	−0.225	−0.849	0.113	−0.349	−0.303	0.579	−0.125
		Matrix Reasoning Child Scaled Score	0.178	0.758	0.064	−0.932	0.107	−0.335	−1.110	0.050	−0.399
Executive functions	CPT2	Detectability T-Score	0.505	0.790	0.053	**3.901**	**0.038**	**0.412**	3.395	0.122	0.359
		Commissions T-Score	1.447	0.432	0.156	**4.861**	**0.008**	**0.524**	3.415	0.088	0.368
	NEPSYII	Auditory Attention Total Corrected Scaled Score	0.075	0.909	0.026	−0.530	0.372	−0.181	−0.605	0.432	−0.207
	WJIII Cognitive	Concept Formation Standard Score	−3.063	0.261	−0.245	−3.326	0.221	−0.266	−0.263	0.921	−0.021
	CMS	Numbers Total Scaled Score	−0.425	0.494	−0.162	0.152	0.782	0.058	0.577	0.340	0.221
Processing speed	WJIII Cognitive	Decision Speed Standard Score	1.100	0.714	0.072	−1.744	0.559	−0.115	−2.844	0.355	−0.187
		Visual Match II Standard Score	−4.181	0.176	−0.282	−2.052	0.479	−0.138	2.130	0.435	0.143
		Processing Speed Standard Score	−2.814	0.356	−0.187	−1.803	0.553	−0.120	1.011	0.684	0.067
Learning and memory	CMS	Word List Total Learning Raw Score	−0.890	0.501	−0.118	−0.455	0.729	−0.061	0.435	0.762	0.058
		Word List Immediate Recall Raw Score	−0.164	0.724	−0.066	0.073	0.875	0.030	0.237	0.665	0.096
		Word List Delayed Raw Score	−0.612	0.197	−0.249	−0.067	0.887	−0.027	0.545	0.294	0.222
		Word List Delayed Recognition Raw Score	**−2.039**	**0.002**	**−0.593**	−0.559	0.391	−0.163	1.480	0.101	0.431
		Dots Location Learning Raw Score	−0.479	0.406	−0.139	−0.348	0.548	−0.101	0.131	0.861	0.038
		Dots Location Total Score Raw Score	−0.469	0.543	−0.103	−1.172	0.136	−0.257	−0.703	0.472	−0.154
		Dots Location Immediate Raw Score	0.005	0.986	0.003	**−0.602**	**0.033**	**−0.373**	−0.607	0.087	−0.376
		Dots Location Delayed Raw Score	0.226	0.432	0.139	**−0.659**	**0.023**	**−0.405**	**−0.886**	**0.021**	**−0.545**

Bold values are statistically significant. CMS, Children's Memory Scale; NEPSY, Neuropsychological Assessment; WASI, Wechsler Adult Scale of Intelligence; WJIII, Woodcock-Johnson III; WPPSI3, Wechsler Preschool and Primary Scale of Intelligence, 3rd edition. *Cohen *d* is calculated based on observed SD at T_{18} pooled across the two groups.

group, the moderate/severe DKA group had increased growth of total and regional GMV and WMV over the 18-month period of the study and lower performance in Full Scale IQ and CPT2 test results (Detectability and Commissions) at the 18-month assessment of this study.

Because brain growth rate varies with age (21) and participants with moderate/severe DKA had higher hyperglycemic indices, analyses were also conducted with subgroups that were matched for age at baseline enrollment and glycemic HbA_{1c} exposure. For these matched subgroups, the growth differences in total and regional GMV and WMV as well as the performance differences in cognitive scores at follow-up became more prominent relative to the overall sample, despite smaller sample size. These structural and cognitive results for the matched subgroups suggest that DKA severity, rather than onset age or 18-month HbA_{1c} exposure, contributes to the observed group differences. In addition, our results indicate that the effects of a moderate/severe episode of DKA are still observable at least 4 years after the occurrence of the metabolic disturbance.

There are limited studies of DKA and its effect on pediatric brain development and cognitive function. The structural brain imaging results of our study are consistent with those previously published (9); namely, there is a different pattern of brain growth, presumably from the time of the DKA episode, in those who experience moderate/severe DKA compared with those who do not. However, the authors found the effects of DKA on brain volume and diffusivity were largely dissipated by 6 months after the DKA event (9), when their study ended. Although our study scanned the children more than 6 months after the DKA episode and the follow-up scan was 18 months from the baseline scan, we found that children who experienced moderate/severe DKA had an increased growth pattern in both total and regional GMV and WMV compared with those who experienced none/mild DKA. Metabolic disturbances associated with DKA may cause acute ischemia/reperfusion of the brain (20,22) or increase in the release of inflammatory factors and cytokines (3,23–25). These physiological changes could, in turn, have lasting effects on brain growth in young children

during a critical time of neurodevelopment. As well, the finding of increased brain growth rate in the group with moderate/severe DKA history might represent neurodevelopmental compensation in those who experienced more neural insult. We do not know whether the differential pattern of brain growth associated with DKA observed here will be sustained, and thus, additional longitudinal follow-up is needed.

We found lower attention performance (i.e., CPT2 scores) in those who experienced moderate/severe DKA compared with the none/mild group, supporting previously published findings that those who experienced an episode of DKA may show cognitive deficits (7,9). Cameron et al. (9) reported lower attention performance scores in those with DKA (defined as venous pH $<$7.3 or bicarbonate $<$15 mmol/L) versus control subjects over 6 months. It is possible that those subjects with moderate/severe DKA in the Cameron et al. (9) study may have also had the lower attention scores. Interestingly, adults up to 5 years out from a moderate/severe traumatic brain injury (14) have lower performance on the same CPT2 subtests of Detectability and Commission as did our participants who experienced moderate/severe DKA. Therefore, deficits in attention may not become detectable until some time after an insult to the developing or mature brain.

Hippocampus structure and function have been related to spatial processing (26) and working memory (27). Our report of lower scores for the Dot Location task in those with moderate/severe DKA history at baseline and at 18 months support previous pediatric studies (5,7) that have found lower spatial processing performance in children with DKA. Interestingly, animal (rat) models of DKA also demonstrate a deficit in object location (28). As shown by Glaser et al. (20) and Hoffman et al. (29), the hippocampus is particularly vulnerable to ischemic/reperfusion of the brain. Recent immunohistochemistry findings show the presence of neuroinflammatory markers in the hippocampus of individuals who died of DKA with and without cerebral edema (29). Therefore, it is notable that we found the moderate/severe group had lower memory performance scores compared with the none/mild group. However, the clinical significance of our memory performance scores requires further investigation because we did not find significant differences in GMV growth rate in the hippocampus. The relationship between lower memory performance, particularly in spatial memory, and hippocampal growth may become evident over time in young children who experience DKA.

Finally, unlike other studies of children with a history of DKA, we found that those with a history of moderate/severe DKA had lower average Full Scale IQ scores compared with the none/mild group 18 months after baseline. The observed 6-point difference in the Full Scale IQ score may not substantially alter functional outcome in the moderate/severe group. However, the effect size for this between-group difference is $\sim$0.5 (Cohen *d*) suggesting the two groups are at least moderately different. Similar to our findings, in a meta-analysis of type 1 diabetes–associated cognitive decline, Tonoli et al. (30) reported decreased executive function performance, Full Scale IQ, and motor speed in children and reduced executive function, Full Scale IQ, motor speed, memory, and spatial memory in adults. Because more significant IQ differences may emerge later in our clinical group, it will be important to continue to monitor these participants with repeated imaging and cognitive testing.

Our study is limited by the relatively small sample size in the moderate/severe DKA group, which may have limited our ability to correlate structural and cognitive changes and to calculate sex or race effects. In addition, we did not perform these studies at the time of diagnosis to assess the acute effect of DKA. Although the between-group differences seen in cognitive performance are statistically significant, the clinical significance is unknown at this time. We used whole-brain VBM analysis, which may be less sensitive to differences in smaller subcortical structures such as the hippocampus. However, the longitudinal nature of the neuroimaging observations and limited cognitive results support the findings and strongly indicate that further follow-up is still necessary.

Although there have been limited longitudinal studies in children after DKA, to our knowledge, this is the first to specifically examine the after effects of moderate/severe DKA in young children and its effect on brain development and cognitive function longitudinally. Our data indicate that even a single episode of moderate/severe DKA in very young children with type 1 diabetes can potentially have long-term effects. Our results suggest that history of DKA and its severity should be included in the analysis of future studies in pediatric type 1 diabetes brain and neuropsychological studies. Recognition of the immediate and longitudinal effect of a history of DKA on the brain further supports the development of programs to screen family members when there is an increased risk of type 1 diabetes to increase awareness of symptoms of type 1 diabetes, reduce the occurrence of DKA at diagnosis, and develop a closed-loop control or islet replacement to prevent further episodes of DKA after diagnosis.

Acknowledgments. The authors are grateful to all of the families who participated in this study.
Funding. This research was supported by the National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (DIRECNET U01-HD-41906, HD-41908, HD-41915, HD-41918, HD-56526, and R01-HD-078463; U54-HD-087011 to the Intellectual and Developmental Disabilities Research Center at Washington University in St. Louis) and by the National Center for Research Resources (5R01-HD-07846305 and UL1-RR-24992 to the Washington University Institute of Clinical and Translational Sciences).
Duality of Interest. N.M. received institutional grant support from Medtronics and LifeScan and is a consultant for PicoLife. S.A.W. is a speaker for Medtronic, Insulet, and Tandem and is a consultant for Sanofi and Zealand. No other potential conflicts of interest relevant to this article were reported.
Author Contributions. T.A., P.K.M., M.J.M., H.S., B.J., and A.L.R. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. N.M. contributed patient data, conducted the studies, and reviewed and edited the manuscript. T.H., A.C., S.A.W., N.H.W., and E.T. reviewed and edited the manuscript. T.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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