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Clinical characteristics of children with cerebral injury preceding treatment of diabetic ketoacidosis

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Clinical Characteristics of Children with Cerebral Injury preceding Treatment of Diabetic Ketoacidosis

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Previous studies have identified more severe acidosis and higher blood urea nitrogen (BUN) as risk factors for cerebral injury during treatment of diabetic ketoacidosis (DKA) in children; however, cerebral injury also can occur before DKA treatment. We found that lower pH and higher BUN levels also were associated with cerebral injury at presentation. *(J Pediatr 2022;250:100-4).*

Cerebral injury occurs in 0.5%-0.9% of DKA episodes in children and is associated with a significant risk of mortality or permanent neurologic morbidity.[1-3] Retrospective studies have documented that cerebral injury is most commonly diagnosed within a few hours of DKA treatment with insulin and intravenous fluids and can present as late as 24 hours after beginning treatment.[2] Previous studies identified biochemical predictors (ie, elevated blood urea nitrogen [BUN] levels, severe acidosis, and hypocapnia) for the development of cerebral injury during DKA treatment.[1-4]

Although evidence of cerebral injury after several hours of treatment for DKA has suggested that such treatment may be responsible for cerebral injury in children, case reports have documented episodes of cerebral injury in children occurring before or very soon after initiation of treatment.[5,6] These cases suggest that factors intrinsic to DKA, rather than treatment-related factors, might be responsible for cerebral injury. Whether children with DKA who present with cerebral injury have unique clinical characteristics has not been investigated previously. We undertook the current study to identify clinical and biochemical factors associated with the occurrence of cerebral injury at presentation and to determine whether these factors differ from those identified as risk factors for cerebral injury later in DKA treatment.

Methods

We performed a secondary analysis of data from the prospective Pediatric Emergency Care Applied Research Network (PECARN) Fluid Therapies Under Investigation in DKA (FLUID) Trial conducted at 13 hospitals during 2011-2017. In addition, we identified patients with DKA episodes with cerebral injury at presentation who were not enrolled in the parent trial owing to availability of research staff or clinician treatment preference over the same period. One site that participated in the PECARN FLUID Trial did not participate in additional data gathering for nonenrolled patients with cerebral injury at presentation. To avoid missing any children with cerebral injury, we also queried electronic medical records at each site using *International Classification of Diseases* codes to identify all children with DKA who

BUN	Blood urea nitrogen
DKA	Diabetic ketoacidosis
ED	Emergency Department
FLUID	Fluid Therapies Under Investigation in DKA
GCS	Glasgow Coma Scale
IL	Interleukin
PECARN	Pediatric Emergency Care Applied Research Network

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were treated with mannitol or hypertonic saline, were intubated, or who died. The study was approved by the Institutional Review Board of each participating hospital with permission for data sharing.

Data Collection for Children with Cerebral Injury at Presentation of DKA

Demographic, clinical (vital signs, presence or absence of headache), and biochemical (glucose, pH, PCO_2, and electrolyte values) data at presentation, as well as cerebral edema treatment (mannitol or hypertonic saline), was abstracted from study forms or medical records. We defined cerebral injury at presentation based on clinical findings sufficient to meet published criteria for DKA-related cerebral injury,[7] and onset of mental status changes (ie, abnormal Glasgow Coma Scale [GCS] score at presentation or other documentation of abnormal mental status at presentation) before beginning treatment for DKA. Strict criteria were used to define cerebral injury, because mental status changes during DKA can result from causes other than cerebral injury (eg, electrolyte imbalance, severe acidosis).[8] Children who had mental status changes or other symptoms suggestive of cerebral injury but never met published criteria for diagnosis of DKA-related cerebral injury were excluded from these analyses. Also excluded were children with mental status changes at presentation who did not meet published criteria for the diagnosis of DKA-related cerebral injury until 6 hours or longer after the start of DKA treatment, as well as those with a condition other than DKA that might result in cerebral injury or that could affect mental status (eg, meningitis, head trauma, alcohol or drug intoxication).

Comparison Group

Data for children with uncomplicated DKA were obtained from the PECARN FLUID Trial database.[9] Methods and results from this trial have been described in detail previously.[9,10] In brief, the trial involved 13 PECARN-affiliated emergency departments (EDs) located in US urban centers. Participants in the FLUID Trial were age <18 years and diagnosed with DKA based on blood glucose >300 mg/dL/16.6 mmol/L, venous pH <7.25 or serum bicarbonate <15 mmol/L, and positive urine or blood test for ketones. Children were excluded from the FLUID Trial if they had disorders that could alter cognitive function (ie, alcohol or drug intoxication, head trauma, or neurologic diagnoses), if they received substantial treatment for DKA prior to arrival at the study site, if they had a low GCS score at presentation (≤11), or if there were clinical scenarios for which the treating physicians felt that specific fluid and electrolyte therapy was required.

FLUID Trial participants were randomized to 1 of 4 intravenous fluid protocols using a 2 × 2 factorial study design. The protocols used either 0.45% or 0.9% NaCl solution infused at either a more rapid or slower rate.[10] Mental status during DKA treatment was monitored by hourly GCS assessment. Diagnoses of clinically apparent cerebral injury (GCS score <14 associated with administration of either mannitol or hypertonic saline, intubation, or death) were recorded. These episodes were reviewed by an adjudication committee to confirm or reject the diagnosis of DKA-related cerebral injury based on the same published criteria used in the present study to identify patients with cerebral injury at presentation.[7] Children enrolled in the FLUID Trial who had abnormal GCS scores or met the criteria for diagnosis of DKA-related cerebral injury during DKA treatment were excluded from the current analyses. Children enrolled in the FLUID Trial who met the criteria for cerebral injury at presentation (defined previously) were included in the current analysis in the cerebral injury at presentation group.

Statistical Analyses

We compared characteristics of children with cerebral injury at presentation of DKA those of to those of children with uncomplicated DKA, as well as those of children who recovered from cerebral injury with and without permanent sequelae, using relative frequencies, means, and SDs. Differences were tested using the Fisher exact test for categorical measures and the Wilcoxon rank-sum test for continuous measures. We described interventions, neurologic function, and outcomes for children with cerebral injury at presentation of DKA using relative frequency and the timing of treatment using median and IQR. We fit a multivariable logistic regression model to the outcome of cerebral injury at presentation of DKA versus uncomplicated DKA, considering all variables that were significantly different between the comparison groups. We selected covariates in order of lowest univariable association sequentially until the next included covariate had a type 3 P value >.05. We excluded colinear covariates in the process, referencing variance inflation factors and the magnitude and direction of adjusted parameter estimates. In sensitivity analyses, we repeated the multivariable analyses after removing DKA episodes in which the occurrence of cerebral injury at presentation was possible but not definite (ie, children presenting with altered mental status who were not treated for cerebral injury until 2-5 hours after beginning DKA treatment; n = 5). We estimated adjusted 95% CIs from the final multivariable logistic model. Analyses were performed using SAS/STAT software version 9.4 (SAS Institute).

Results

We identified 106 DKA episodes in which children had altered mental status at presentation of DKA and were treated with mannitol or hypertonic saline, were intubated, or died. Of these, 50 (47.2%) met the criteria for DKA-related cerebral injury.[7] Among these 50 DKA episodes, we excluded 2 in which published criteria for DKA-related cerebral injury were met more than 6 hours after beginning DKA treatment. Five more episodes were treated for cerebral injury between 2 and 5 hours after presentation. These children were included in the main analyses but excluded in sensitivity analyses. The remaining 43 children met the published criteria for DKA-related cerebral injury and were treated for cerebral injury within 2 hours of ED presentation. Data from children with cerebral injury at presentation were compared with data from 1227 children with uncomplicated

Table I. Characteristics of cerebral injury and uncomplicated DKA cohorts

Characteristics	Cerebral injury at presentation (N = 48)	Uncomplicated DKA (N = 1227)	*P* value
Age, y, mean (SD)	9.7 (4.7)	11.2 (4.0)	.03
Male sex, n (%)	20 (41.7)	575 (46.9)	.56
Diabetes history, n (%)			>.99
New-onset diabetes	23 (47.9)	586 (47.8)	
Previously diagnosed diabetes	25 (52.1)	641 (52.2)	
Laboratory values at presentation, mean (SD)			
Glucose, mg/dL	759 (445)	514 (146)	<.001
Glucose-corrected sodium, mEq/L	146.4 (12.0)	141.2 (5.0)	.006
Potassium, mEq/L	4.8 (1.3)	4.9 (1.0)	.47
Chloride, mEq/L	102.4 (10.4)	99.3 (6.1)	.09
Bicarbonate, mEq/L	6.1 (2.9)	9.0 (3.2)	<.001
BUN, mg/dL	29.6 (18.1)	16.5 (7.2)	<.001
Creatinine, mg/dL	1.2 (0.8)	0.7 (0.3)	<.001
pH	6.94 (0.14)	7.17 (0.10)	<.001
pCO_2, mm Hg	25.0 (9.8)	26.1 (7.2)	.32
Clinical symptoms, n (%)			
Headache at presentation	7 (14.6)	264 (21.5)	.29
Vital signs at presentation, mean (SD)			
Systolic blood pressure, mm Hg	117.1 (22.6)	118.5 (15.0)	.17
Diastolic blood pressure, mm Hg	73.3 (19.7)	71.7 (11.8)	.02
Heart rate, bpm	132.3 (19.8)	116.8 (20.9)	<.001
Respiratory rate, breaths/minute	31.2 (11.2)	24.4 (6.7)	<.001

pCO_2, partial pressure of carbon dioxide.
P values are from the Fisher exact test (sex, diabetes history, headache) and Kruskal–Wallis test (all others); tests of differences in blood pressure and heart rate were performed on *z*-scores adjusting for age, sex, and height (blood pressure).
Missing data for (cerebral injury at presentation, uncomplicated DKA): sodium (0, 2), potassium (0, 1), chloride (1, 1), bicarbonate (3, 0), BUN (0, 3), creatinine (1, 2), pH (0, 3), pCO_2 (0, 4), systolic blood pressure (1, 2), diastolic blood pressure (1, 2), heart rate (0, 2), and respiratory rate (0, 2).

Table II. Characteristics of cerebral injury cohort by outcome

Characteristics	Recovered (N = 40)	Disability/death (N = 8)	*P* value
Age, y, mean (SD)	9.7 (4.7)	9.8 (4.8)	.88
Male sex, n (%)	18 (45.0)	2 (25.0)	.44
Diabetes history, n (%)			>.99
New-onset diabetes	19 (47.5)	4 (50.0)	
Previously diagnosed diabetes	21 (52.5)	4 (50.0)	
Laboratory values at presentation, mean (SD)			
Glucose, mg/dL	715 (434)	982 (460)	.09
Glucose-corrected sodium, mEq/L	145.4 (11.5)	151.2 (14.0)	.29
Potassium, mEq/L	5.0 (1.3)	3.7 (0.7)	.006
Chloride, mEq/L	101.4 (9.2)	108.3 (15.4)	.39
Bicarbonate, mEq/L	6.3 (3.2)	5.4 (1.5)	.51
BUN, mg/dL	26.8 (16.6)	43.6 (20.3)	.006
Creatinine, mg/dL	1.1 (0.7)	2.1 (0.9)	.005
pH	6.96 (0.12)	6.81 (0.17)	.01
pCO_2, mm Hg	25.0 (9.1)	25.4 (13.4)	.73
Clinical symptoms, n (%)			
Headache at presentation	6 (15.0)	1 (12.5)	>.99
Vital signs at presentation, mean (SD)			
Systolic blood pressure, mmHg	118.8 (23.5)	107.6 (14.4)	.22
Diastolic blood pressure, mmHg	75.3 (18.8)	62.3 (22.6)	.24
Heart rate, bpm	133.6 (17.7)	125.6 (28.8)	.50
Respiratory rate, breaths/minute	32.2 (11.9)	26.1 (4.7)	.15
Interventions, n (%)			
Mannitol	30 (75.0)	4 (50.0)	.21
Hypertonic saline	17 (42.5)	6 (75.0)	.13
Endotracheal intubation	12 (30.0)	8 (100.0)	<.001

P values are from the Fisher exact test (sex, diabetes history, headache, interventions) and the Kruskal–Wallis test (all others); tests of differences in blood pressure and heart rate were performed on *z*-scores adjusting for age, sex, and height (blood pressure).
Missing data for (recovered, disability/death): chloride (0, 1), bicarbonate (3, 0), creatinine (0, 1), systolic blood pressure (0, 1), diastolic blood pressure (0, 1).

DKA from the FLUID Trial who had normal mental status at presentation and throughout treatment.

Children with cerebral injury at presentation of DKA had a median GCS score at presentation of 9.5 (IQR, 7-11). Forty children (83.3%) recovered without apparent neurologic deficits, 6 (12.5%) had permanent neurologic disability after recovery, and 2 (4.2%) died. Mannitol was used to treat cerebral injury in 34 (71%) and hypertonic saline in 23 (48%); 12 received both therapies. Twenty children (42%) presenting with cerebral injury required intubation. Most children received therapy for cerebral injury within 1 hour of starting DKA treatment (median time to cerebral injury treatment, 20 minutes; IQR, 8-51 minutes).

Compared with children with uncomplicated DKA, those presenting with cerebral injury were younger and had a higher heart rate, diastolic blood pressure, and respiratory rate (Table I). Children with cerebral injury at presentation also had lower pH and bicarbonate levels and higher glucose, glucose-corrected sodium, BUN, and creatinine levels. Complaints of headache were recorded with similar frequency in the 2 groups. In multivariable analyses, only pH (aOR, 0.21, 95% CI, 0.15,0.29; $P < .001$) and BUN (aOR, 1.09; 95% CI 1.06,1.12; $P < .001$) retained a significant association with cerebral injury at presentation. In a sensitivity analysis, we removed children who presented with altered mental status but were not treated for cerebral injury until later in the course of DKA treatment (2-5 hours after beginning treatment; n = 5). Results of these analyses were nearly identical to those of the main analysis (aOR [95% CI]: pH, 0.21 [0.15,0.30]; BUN, 1.09 [1.06,1.12]).

When we compared children who recovered from cerebral injury without apparent sequelae (n = 40) with those who died or survived with neurologic deficits (n = 8), we found that children with adverse outcomes presented with more severe acidosis, as well as higher BUN and creatinine levels (Table II). In addition, children with adverse outcomes had significantly lower potassium levels at presentation. There were no significant differences in the type of hyperosmolar therapy used in the 2 groups.

Discussion

We characterized clinical findings in children with symptoms and signs of DKA-related cerebral injury at the time of presentation to the ED. We found that lower pH and higher BUN levels were significantly associated with cerebral injury at presentation, after adjusting for other clinical and biochemical variables. Previous studies have primarily described children with

DKA who were later diagnosed with cerebral injury during treatment with insulin and intravenous fluids. These studies also found that greater acidosis (lower pH and pCO_2) and elevated BUN concentrations were the main indicators of risk of cerebral injury during treatment.[1-4] These same factors (more severe acidosis and higher BUN concentrations at presentation) also distinguished children who developed adverse outcomes of cerebral injury in the current study from those who recovered from cerebral injury without sequelae. These findings are consistent with the hypothesis that factors intrinsic to the DKA episode and not treatment-related factors are likely responsible for DKA-related cerebral injury.

The cause of DKA-related cerebral injury continues to be a subject of debate and investigation. Initial reports suggested that rapid infusion of intravenous fluids might cause brain cell swelling, resulting in increased intracranial pressure and cerebral injury.[11,12] As a result, many pediatric DKA guidelines recommended limiting fluid bolus administration and rehydrating slowly over a prolonged period. These recommendations came into question as accumulating data suggested etiologies other than fluid infusion and osmotic change might be responsible for DKA-related cerebral injury. Several case reports have documented the occurrence of cerebral injury at the time of ED presentation both before and shortly after the start of DKA treatment, suggesting that cerebral injury could occur in the absence of substantial intravenous fluid infusion.[5,6] Furthermore, a case series describing children with severe DKA-related cerebral injury documented that cerebral imaging studies often showed no evidence of edema at the time of diagnosis of cerebral injury, with edema and other signs of brain injury (eg, hemorrhage, infarction) often developing hours or days later.[7] Finally, the PECARN FLUID Trial found no associations between rapid fluid infusion and the frequency of mental status changes or clinical diagnoses of cerebral injury during DKA treatment.[9] Although these and other data strongly suggest that rapid fluid infusion is not responsible for DKA-related cerebral injury, the possible involvement of other treatment-related factors has been unclear. Children presenting with DKA-related cerebral injury in the absence of treatment for DKA provide important information about the pathophysiology of this complication. Identification of similar risk factors in these children compared with those who develop cerebral injury later during treatment suggests similar pathophysiologic causes in both groups and points away from the involvement of treatment-related factors.

Notably, children who had adverse outcomes of cerebral injury had lower potassium levels than those who recovered without sequelae, despite more severe renal dysfunction. This finding may reflect more prolonged illness in these children with greater total body potassium losses. Alternatively, lower potassium levels might reflect failure of normal cellular ion-exchange mechanisms.

Recent data suggest that DKA causes neuroinflammation that might be responsible for brain injury.[13] DKA is characterized by marked systemic elevations in levels of inflammatory cytokines and chemokines, including interleukin (IL)-1, IL-6, IL-10, tumor necrosis factor α, interferon-γ, and C-X-C motif chemokine ligand 1, as well as endothelial activation (elevated levels of soluble intercellular adhesion molecule 1 and vascular adhesion molecule 1).[13-16] DKA also may impair blood-brain barrier function by causing alterations in matrix metalloproteinases, allowing fluid and blood-borne proinflammatory or neurotoxic proteins to invade the central nervous system.[17,18] In animal models, cellular findings indicative of neuroinflammation, such as activation of brain microglia and reactive astrogliosis, also have been documented during DKA treatment, along with increased levels of proinflammatory cytokines in brain tissue lysates.[13,19,20]

There are some limitations to the current study. The duration of symptoms prior to ED presentation was not analyzed, because this information frequently was unavailable in the medical records or was inexact. This information would provide helpful evidence as to whether cerebral injury at presentation is related to prolonged duration of untreated DKA. Of note, comparisons of children with and without adverse outcomes of cerebral injury showed significantly lower potassium levels at presentation in those with adverse outcomes. These data suggest greater electrolyte deficits in children who develop adverse outcomes that may be caused by more prolonged duration of DKA prior to seeking treatment.

Our current data demonstrate that children with DKA presenting to the ED with cerebral injury have clinical characteristics similar to those previously described in children who develop cerebral injury during DKA treatment. These findings provide further evidence that physiologic alterations intrinsic to DKA, such as neuroinflammation, are likely responsible for DKA-related cerebral injury. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Are We Any Better at Understanding the Prognosis of Immunoglobulin A Vasculitis Nephritis?

Hurley RM, Drummond KN. Anaphylactoid purpura nephritis: clinicopathological correlations. J Pediatr 1972;81:904-11.

Glomerulonephritis is perhaps the most worrisome manifestation of immunoglobulin A vasculitis (IgAV; previously named Henoch–Schönlein or anaphylactoid purpura), and nephrologists have struggled for many years with how to best understand the course of the illness and its ultimate prognosis. One of the earliest attempts to relate clinical features to outcomes was made by Hurley and Drummond, who carefully detailed the clinical course, histologic findings, and kidney outcomes of a cohort of 31 children with IgAV seen at their institution. A major contribution of this work was the finding that nephritis may occur quite late in the course of IgAV, meaning that follow-up for the development of nephritis needs to be continued beyond resolution of the rash and other extrarenal manifestations of IgAV. They were unable to establish a clear clinicopathologic relationship between kidney biopsy findings and outcome, however, perhaps because of the incomplete understanding at that time of the role of the immunologic mechanisms that underlie IgAV.

In the 50 years that have passed since the publication of Hurley and Drummond's report, many other investigators have tried to develop prediction tools for IgAV nephritis. Although Hurley and Drummond were unable to establish a correlation between the extrarenal manifestations of IgAV and what is going on in the kidney, contemporary investigators have not abandoned that line of inquiry. Recently, it was reported that a more comprehensive assessment of IgAV using the Pediatric Vasculitis Activity Score at least enabled prediction of which patient with IgAV was likely to develop nephritis.[1] In addition, a recent Systematic Review has identified novel urinary biomarkers (beyond proteinuria) that could potentially be used to predict the severity of immunoglobulin A nephritis.[2] The question that remains unanswered, even 50 years after Hurley and Drummond's report, is whether these novel predictive tools can be used to develop improved therapies that will make development of nephritis a less worrisome feature of IgAV.

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