Risk Factors for Cerebral Edema and Acute Kidney Injury in Children with Diabetic Ketoacidosis

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Abstract

Objectives: To study the clinical profile and risk factors of cerebral edema and acute kidney injury in children with diabetic ketoacidosis.

Design: Retrospective review of medical records.

Patients: Fifty consecutive patients (age <18 years) admitted to our pediatric intensive care unit with a diagnosis of diabetic ketoacidosis over 5 years.

Materials and methods: Retrospective analysis of medical records was done, and data including patients' age, sex, presenting features, biochemical profile including blood glucose, osmolality, urea, creatinine, and venous blood gas, electrolytes were recorded at admission, at 12 and 24 hours. Treatment details including fluid administration, rate of fall of glucose, time to resolution of diabetic ketoacidosis were noted. Complications such as cerebral edema and acute kidney injury were recorded. Patients with and without cerebral edema and acute kidney injury were compared. Variables that were significant on univariate analysis were entered in a multiple logistic regression analysis to determine the independent predictors for cerebral edema and acute kidney injury. Odds ratio and 95% confidence interval were calculated using SPSS version 22.

Measurements and main results: Between November 2015 and 2020, 48 patients were admitted for a total of 50 episodes of diabetic ketoacidosis. Two patients had recurrent diabetic ketoacidosis. Median age was 9.5 years (range 1–17). Thirty-one patients (62%) had new-onset type I diabetes mellitus. Twenty-two patients (44%) presented with severe diabetic ketoacidosis. Cerebral edema and acute kidney injury were seen in 11 (22%) and 15 (30%) patients, respectively. On multiple logistic regression analysis, higher blood urea level, lower serum bicarbonate level, and higher corrected sodium levels at admission were identified to be variables independently associated with risk of cerebral edema.

Conclusions: Higher corrected sodium, higher urea level, and lower serum bicarbonate levels at admission are predictive of cerebral edema in patients presenting with diabetic ketoacidosis. The severity of dehydration and acidosis in DKA appears to be a common factor responsible for the development of dysfunction of both brain and kidney.

Keywords: Acute kidney injury (AKI), Cerebral edema (CE), Diabetic ketoacidosis (DKA), Pediatric.

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Introduction

Diabetic ketoacidosis (DKA) is a serious complication of type I diabetes, which can be potentially life-threatening. It is a complex metabolic state characterized by dehydration, acidosis, and dyselectrolytemias. The incidence of pediatric-onset diabetes and DKA is slowly rising.[1] Prolonged or complicated DKA can lead to organ dysfunction, prolonged hospitalization, and increased cost of treatment. Cerebral edema (CE) is a rare but extremely dreaded complication in DKA with mortality rates of 20–90% reported in various series in the past.[2] While the mortality has reduced considerably in recent times, with newer series reporting rates of less than 1%, CE is still the leading cause of death in DKA.[3] Also, of growing concern is the adverse impact it has on the neurocognitive outcomes of children.[4]

Acute kidney injury (AKI) is a common occurrence, especially in severe DKA.[5] There is a growing interest in the risk factors, pathogenesis, and consequences of AKI in patients with DKA. It has been linked to progressive chronic kidney disease and subtle cerebral injury.[6]

In our observational study, we studied the clinical profile of pediatric patients with DKA and the incidence of these two main complications—namely CE and AKI. We also attempted to identify risk factors responsible for their development. A secondary objective was to compare the clinical presentation of patients with new-onset diabetes and known diabetes.

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Methods

This was a retrospective study, which included all patients (age <18 years) who were admitted to the pediatric intensive care unit in our hospital with DKA between November 2015 and 2020.

The International Society for Pediatric and Adolescent Diabetes 2014 and 2018 guidelines were used for the diagnosis of DKA and to grade the severity.[7] The age, sex, presenting features, and comorbidities were noted. Laboratory parameters including venous blood gas parameters, electrolytes (sodium, potassium, chloride) were recorded at admission and at 12 and 24 hours. Serum osmolarity, white blood cell (WBC) count, and septic screen (in patients with fever) were also noted at admission. Fluid therapy was administered in accordance with the International Society for Pediatric and Adolescent Diabetes 2014 and 2018 guidelines.[7] Rate of fluid administration, time to resolution of DKA, and time to achieve glycemic control (blood glucose <200 mg/dL) were recorded. The presence of complications such as CE, AKI, fluid refractory shock, and thrombosis was noted. CE was identified using the criteria described by Muir et al.[8] AKI was defined and staged using the 2012 Kidney Disease/Improving Global Outcomes criteria.[9] Patients with and without CE were compared, using means and SDs for continuous variables and frequencies and percentages for categorical variables. Similar comparison was done for patients with and without acute kidney injury. Continuous variables were compared using student's "*t*"-test, and categorical variables were compared using Chi-square test. Risk factors for CE and AKI were independently identified using univariate analysis. The significant risk factors were entered into multivariate forward logistic regression analysis to identify predictors for CE and AKI. SPSS version 22 was used for statistical analysis.

Results

A total of 50 episodes of DKA in 48 patients were studied. The median age was 9.5 years (range 1–17), and 26 patients (52%) were male. Recurrent DKA occurred in two patients, both girls aged 10 and 14 years. In both, the second episode occurred within a year of the first and was precipitated by missed insulin doses and additionally by infection in one. The comorbidities found included celiac disease in six (12%) and hypothyroidism in four patients (8%).

Patients with new-onset diabetes presented more often with DKA ($n = 31$; 62%) compared to patients with known type I diabetes ($n = 19$; 38%) (Table 1). All patients with known type I diabetes were on basal bolus regimen except one patient who was on insulin pump therapy. The duration of symptoms was significantly higher in those with new-onset diabetes (median 10 days; 7, 21) compared to patients with known diabetes (median 3 days; 1, 4; $p < 0.001$). Patients with known diabetes had significantly higher white blood cell (WBC) count at presentation (mean 20417.4 µL, SD 1170.2 vs 12986.1 µL, SD 765.7; $p = 0.02$). Glycosylated hemoglobin levels were high both in patients with new-onset diabetes (mean 12.8, SD 2.2) and known diabetes (mean 12.6, SD 2.2). There was no significant difference in glycosylated hemoglobin, severity of DKA, or time to resolution in both the groups (Table 1).

Twenty patients (40%) had history of fever at time of presentation and were started on empiric antibiotic therapy. Among these 20 patients, focus of infection was found in 16 (80%) on clinical examination and/or investigations. Respiratory tract infections were most commonly seen in 25% of patients with fever. Fungal infections were found in four patients including oral candidiasis ($n = 2$), fungal urinary infection ($n = 1$), and gastrointestinal mucormycosis ($n = 1$). One patient had dengue fever. Culture positivity was present in six patients, out of which four had bacterial growth (urine, ear discharge, endotracheal aspirate) and two had fungal growth (urine, resected intestinal specimen). Blood culture of all the patients was sterile.

Severe DKA (pH <7.1) was seen in 22 episodes (44%). Mild (pH 7.2–7.3) and moderate DKA (pH 7.1–7.2) were seen in 11 (22%) and 17 episodes (34%), respectively. Insulin infusion was used in all except three patients who were managed with subcutaneous insulin

Table 1: Clinical profile of total patients of DKA and comparison of patients with known diabetes vs new-onset diabetes

Parameter	*Total* *N = 50*	*New-onset diabetes* *n = 31*	*Known diabetes* *n = 19*	*p value*
Age (years)	9.5 (5.8–13)	8 (5–11)	11 (8–14)	0.08
Duration of symptoms (days)	7 (3–14)	10 (7–21)	3 (1–4)	<0.001
pH	7.1 (0.2)	7.1 (0.2)	7.1 (0.1)	0.53
Bicarbonate at admission	7.6 (4.1)	7.3 (4)	8 (4.3)	0.58
pCO_2 at admission (mm Hg)	17.7 (5.2)	16.7 (5.0)	19.4 (5.1)	0.07
Sodium at admission (mEq/L)	136.8 (5.9)	137.4	135.8	0.29
Potassium at admission (mEq/L)	4.3 (0.7)	4 (0.6)	4.6 (0.9)	0.04
Blood glucose at admission (mg/dL)	487.4 (162.6)	512.2 (180.9)	447 (121)	0.17
WBC (cells/µL)	15810 (997)	12986 (765)	20417 (1170)	0.02
Glycosylated (Hb%)	12.7 (2.2)	12.8 (2.2)	12.6 (2.2)	0.77
Osmolarity (mOsm/kg)	310.2 (19.1)	312.2 (22.4)	307 (11.8)	0.29
Fluid rate (mL/kg/hour)	90.1 (18.4)	91.9 (20)	87.1 (15.6)	0.37
Rate of blood glucose decline (mg/dL/hour)	37.7 (17.3)	38.6 (20)	36.4 (11.7)	0.67
Resolution time (hours)	21.8 (14.2)	24.2 (16.4)	17.8 (8.6)	0.12
Time to glycemic control blood glucose <200 mg/dL (hours)	7.9 (3.9)	8.6 (4.3)	6.7 (2.6)	0.10
ICU stay (days)	2 (1–2)	2 (1–3)	1 (1–2)	0.2
Hospital stay (days)	3 (2–5)	4 (2–5)	3 (2–4)	0.17

Data presented as mean (SD) and median (IQR)

due to mild severity of DKA. During correction of ketoacidosis with fluids and insulin, nearly half (23 patients, 46%) required a glucose infusion rate of more than 4 mg/kg/minute for achieving controlled fall in blood glucose.

Dyselectrolytemias were noted in the form of hypernatremia ($n = 6$, 12%), hypokalemia ($n = 23$, 46%), hyperkalemia ($n = 7$, 14%), and hyperchloremia >120 mEq/L ($n = 13$, 26%). Hypoglycemia (blood glucose level <70 mg/dL) occurred in three patients.

The complications observed included CE in 11 patients (22%) and AKI in 15 patients (30%). Other complications observed included shock requiring vasopressors in four patients (8%), deep venous thrombosis, multiple brain infarcts, and mucormycosis in one patient each. Elevated lipase levels were found in eight patients (16%), with highest value 6162 U/L recorded in one patient. Five patients (10%) had greater than threefold elevation in lipase level; however, none had ultrasonographic evidence of pancreatitis. Four patients (8%) required invasive ventilatory support for respiratory failure.

CE AND DKA

Patients with CE had significantly higher incidence of infections (72.7 vs 23.1%; $p = 0.004$), higher serum glucose (576.6 mg/dL, SD 218.3 vs 462 mg/dL, SD 133.7; $p = 0.034$), and higher corrected sodium (151.9 mEq/L, SD 9.4 vs 142.5, SD 5.1; $p = 0.08$). Time to resolution of DKA and time to glycemic control were significantly longer in the CE group (Table 2). There was no difference in age, sex, glycosylated hemoglobin levels, or previously known diabetes status between the patients with or without CE. On univariate analysis, we found that patients with CE had higher PRISM score and a worse biochemical profile at presentation including lower pH, higher blood glucose, higher corrected sodium level, and higher chloride levels. Fluid administration rates were higher in patients with CE compared to those without [OR 1.12 (95% CI 1.05–1.2), $p = 0.01$]. Rate of fall of sugar in CE group was similar to the non-CE group [OR 98 (95% CI 0.94–1.03), $p = 0.442$] (Table 3). On multivariate logistic regression, higher urea, higher corrected sodium, and lower

Table 2*: Comparison of a. CE vs non-CE groups. b. AKI vs non-AKI groups

	With CE group (n = 11)	*Without CE group (n = 42)*	*p value*	*AKI group (n = 15)*	*Non-AKI group (n = 35)*	*p value*
Age (years)	8 (5–11)	10 (7–14)	0.109	8 (5–11)	10 (8–14)	0.02
Females (*n*)	6 (54.5)	18 (46.2)	0.74	7 (46.7)	17 (48.6)	0.10
New-onset diabetes (*n*)	8 (72.7)	23 (59.0)	0.50	8 (25.8)	23 (74.2)	0.53
Infection focus (*n*)	8 (72.7)	9 (23.1)	0.004	9 (60.0)	8 (22.9)	0.02
Blood glucose at admission (mg/dL)	576.6 (218.3)	462 (133.7)	0.03	561.9 (204.0)	455.5 (132.2)	0.03
PRISM score	20.2 (6.5)	8.9 (2.9)	<0.001	16.5 (7.9)	9.2 (3.5)	<0.001
Glycosylated hemoglobin %	12.2 (2.5)	12.9 (2.1)	0.38	12.1 (2.6)	13.0 (2.0)	0.18
pH	6.9 (0.1)	7.1 (0.1)	<0.001	6.9 (0.1)	7.1 (0.1)	<0.001
Bicarbonate at admission (mmol/L)	4.4 (3)	9.2 (5.2)	0.005	4.7 (3.0)	8.8 (3.9)	0.001
pCO_2 at admission (mm Hg)	13 (3.8)	20.1 (6.7)	0.001	14.4 (4.5)	19.1 (4.9)	0.002
Corrected sodium at admission (mEq/L)	151.9 (9.4)	142.5 (5.1)	0.008	148.0 (9.6)	143.1 (5.7)	0.03
Urea at admission (mg/dL)	39 (30)	23.1 (12.8)	0.11	41.7 (26.3)	20.1 (9.1)	0.007
Osmolarity at admission (mOsm/kg)	330.7 (25)	304.4 (12.3)	0.006	323.7 (23.4)	304.3 (13.6)	0.008
WBC cells (µL)	19868 (998)	14264 (972)	0.10	24600 (1190)	12000 (590)	0.001
Maximum sodium (mEq/L)	145 (7.2)	138.3 (3.2)	0.01	142.5 (6.7)	138.5 (4.6)	0.02
Maximum chloride (mEq/L)	122.5 (7)	113.8 (8.3)	0.03	119.4 (7.7)	114.6 (8.6)	0.07
12 hours bicarbonate (mmol/L)	9 (2)	13 (4.6)	0.01	8.6 (3.1)	13.6 (4.1)	<0.001
12 hours chloride (mEq/L)	120.4 (7)	111.7 (7.4)	0.01	117.4 (7.9)	111.9 (7.7)	0.03
24 hours bicarbonate (mmol/L)	13.3 (3)	17.6 (4.4)	0.01	12.8 (3.0)	18.3 (4.0)	<0.001
24 hours chloride (mEq/L)	116.2 (7.6)	106.8 (6.3)	<0.001	112.5 (9.1)	107.3 (6.4)	0.03
Fluid rate (mL/kg/24 hour)	111.8 (18.3)	84.0 (13.1)	<0.001	103.3 (19.8)	84.4 (14.6)	0.003
Rate of blood glucose decline (mg/dL/hour)	38.7 (18.9)	34.2 (9.3)	0.45	34.7 (9.2)	39 (19.7)	0.43
Vasoactive drugs (*n*)	3 (27.3)	1 (2.6)	0.03	3 (20.0)	1 (2.9)	0.08
Resolution time (hours)	37.5 (19.4)	16.5 (9)	0.005	33.7 (17.8)	16.6 (8.4)	0.003
Time to glycemic control (hours)	11.8 (4.7)	6.7 (2.8)	<0.001	10.2 (4.1)	6.9 (3.3)	0.004
ICU stay (days)	3 (2–7)	2 (1–2)	<0.001	2 (2–7)	1 (1–2)	0.002
Hospital stay (days)	5 (3–13)	3 (2–4)	0.003	4 (3–9)	3 (2–4)	0.003

*Data presented as mean (SD) and median (IQR) for continuous variables and number (percentage) for categorical variables

serum bicarbonate levels were identified as independent variables associated with higher risk of developing CE (Table 3).

AKI and DKA

AKI was present in 15 (30%) patients, out of which 14 (93.3%) patients had AKI at the time of admission. One patient developed AKI 24 hours after admission. Stage 1 and 2 AKI were seen in 13 patients (26%), which resolved spontaneously with fluid correction. Two patients (4%) had stage 3 AKI, and both required renal replacement therapy in the form of sustained low efficiency dialysis. On univariate analysis, older age, focus of infection, worse biochemical profile at presentation (including lower pH, higher blood glucose), higher corrected sodium, higher PRISM score, higher 12-hour chloride levels were variables associated with risk of AKI.

Discussion

DKA in children is often the initial presentation of type I diabetes, more so in developing countries. The worldwide frequency of DKA at diagnosis of type I diabetes has been reported to range from 12.8 to 80%.[10] Diagnosis is often delayed at the first presentation. In our study too, we found the duration of symptoms to be much longer in patients with new-onset diabetes compared to those with known diabetes. Poor glycemic control is a risk factor, which precipitates DKA in patients with known diabetes.[11] This is supported by the fact that we found no significant difference in the glycosylated hemoglobin levels between patients with new-onset diabetes (in whom high levels are expected) and patients with known diabetes.

The other common precipitant is infection. Fever is usually considered to be a sign of underlying infection in DKA and thus an indication to start empiric antibiotic therapy. Interestingly, we found that while 40% of patients presented with fever, only 8% of patients had positive bacterial culture growth, while fungal infections also had similar occurrence (8%). Hence, when a patient with DKA presents with fever, starting an empiric antibiotic is not sufficient; a careful survey to identify the correct source and type of infection is warranted. In fact, a thorough search for a focus of infection should be carried out in every case of DKA, as patients with DKA may be normothermic or mildly hypothermic, irrespective of the presence of infection.[12]

It is known that leukocytosis may occur in DKA, and while it is clear that decision to initiate antibiotic should not be based on leukocyte count alone, the reason why it occurs in DKA is not clearly known, though many theories have been postulated.[13,14] We found that leukocytosis was significantly higher in patients with known diabetes compared to new-onset diabetes; however, its clinical relevance is unclear.

DKA can be reversed only by administering appropriate fluids and insulin, and the usual target rate of decline of glucose is 50–100 mg/dL/hour. If the rate of decline is more, the preferred strategy would be to increase the dextrose concentration of the administered fluid, rather than decreasing insulin infusion rate, which is essential for reversal. Nearly half of our patients required increasing the glucose infusion rate to maintain a steady fall in glucose levels.

The acidosis and dehydration in DKA can lead to organ dysfunction. DKA is also associated with an elevated level of active systemic inflammatory processes and oxidative stress.[15] Newer studies have shown that the incidence of organ injuries in children with DKA is much higher than previously thought.[4]

The common organ dysfunction we observed in our patient cohort was the involvement of the brain and kidney. Hypotension

Table 3: Cerebral edema: univariate and multivariate analysis

	Univariate		*Multivariate*	
Risk factor	*Odds ratio (95% CI intervals)*	*p value*	*Odds ratio (95% CI intervals)*	*p value*
Age	0.85 (0.71–1.02)	0.077		
Sex	1.4 (0.37–5.37)	0.624		
Known diabetes	0.54 (0.12–2.35)	0.411		
Infective focus	8.89 (1.94–40.71)	0.005		
PRISM score	1.73 (1.24–2.43)	0.001		
Blood glucose at admission	1.0 (1.0–1.01)	0.074		
Glycosylated hemoglobin	0.87 (0.64–1.18)	0.382		
Urea	1.04 (1.0–1.09)	0.043	1.06 (1.01–1.11)	0.04
Baseline pH	0.00 (0.00–0.02)	0.001		
Bicarbonate at admission	0.72 (0.56–0.92)	0.009	0.65 (0.43–0.98)	0.04
Corrected sodium at admission	1.24 (1.07–1.44)	0.004	1.17 (1.01–1.36)	0.04
Chloride at admission	1.14 (1.03–1.26)	0.010		
12 hours chloride	1.18 (1.04–1.33)	0.008		
Glucose infusion rate >4 mg/kg/minute	7.71 (1.46–40.90)	0.016		
Osmolarity	1.1 (1.03–1.06)	0.003		
Time to glycemic control	1.69 (1.16–2.45)	0.006		
Resolution time	1.15 (1.05–1.27)	0.004		
AKI	12.19 (2.57–57.94)	0.002		
Rate of glucose decline	0.98 (0.94–1.03)	0.442		
Fluid rate	1.12 (1.05–1.20)	0.001		

was uncommon, and in most cases, fluid therapy was sufficient to correct shock; only 8% of patients required vasoactive agents, and this finding is similar to other pediatric studies.[16] However, the incidence of fluid refractory shock has been reported to be higher in a few studies, where the number of patients with sepsis was higher.[17] It is difficult to distinguish hypovolemic from septic shock in DKA, as usual clinical signs of volume contraction are not obvious due to hyperosmolar state. Also, traditional signs of shock such as tachycardia, prolonged capillary refill, dull sensorium could be due to a myriad of other factors such as acidosis, dehydration, and CE.[18] While DKA can be rarely associated with pancreatitis, more often isolated elevations in lipase and/or amylase are seen. This has been reported to occur in 16–25% of cases.[19] We observed the same in our study cohort; however, none of the cases, even those with more than threefold elevation, had pancreatitis.

CE is the most dreaded complication of DKA. It usually occurs after a few hours of treatment initiation, but may be present at times even before starting treatment. The diagnosis is essentially clinical, and it should be suspected if there is a sudden deterioration in neurological status or if comatose state persists despite treatment.[2] Muir et al. outlined the traditional definitive criteria for diagnosis of CE, which is clinically based; hence, we used it in our study.[8] Most studies, especially from developed countries, report the incidence of CE to be <1%.[20] Twentyfold higher incidence has been reported from Indian centers, which cater to the sickest of patients.[17,21] The incidence of CE in DKA in our study too was high, possibly as ours is a referral tertiary care center. Variations in the criteria used for defining CE may account for the difference in incidence in various studies. We observed that patients who developed CE were sicker at presentation, with more severe acidosis, higher urea levels reflecting higher degree of dehydration. Similar risk factors have been reported in previous studies.[22] Also, patients with CE were noted to have higher corrected sodium levels at presentation. Hence, hypernatremia at admission may be considered as a red flag for the development of CE in patients with DKA. The patients who developed CE received higher fluid rates; however, since the sample size is small, it is difficult to comment if there is a causal relation between the two, or whether both high fluid requirement and CE are the result of the higher severity of DKA. A large multicentric randomized controlled trial demonstrated that rate of fluid administration did not significantly influence the neurological outcomes in children with DKA.[23]

We observed that AKI was more common than CE. AKI had incidence of 30%, which is comparable to other studies in children.[24,25] While we observed that most patients had AKI at presentation, it can sometimes develop 12–24 hours later, or progress after treatment is initiated, thereby fuelling the reperfusion injury theory. We found that severity of DKA was a significant factor, which determines AKI, suggesting that dehydration and acidosis may play a role in its development. As hypothesized for CE, apart from dehydration causing pre-renal AKI, it is possible that the underlying diffuse inflammatory process of DKA may be an important factor leading to intrinsic AKI. There has been a great interest in the influence of hyperchloremia on the development of AKI; however, its exact role in the pathogenesis of AKI is unclear.[26] A recent double-blind randomized controlled trial comparing Plasma-Lyte (lower chloride content) and saline in DKA found no significant difference in the incidence or progression of AKI with the use of either fluid.[27] We could not find any meaningful association of serum chloride level or any other factor with AKI on multivariate analysis.

We observed that higher urea and lower bicarbonate levels were risk factors for the development of CE. These risk factors have also been reported by previous Indian studies.[17] A recent study demonstrated that children with AKI had lower scores on short-term memory tests during DKA and lower scores on neurocognitive testing, 3–6 months after recovery from DKA, implying that mechanisms for the development of both these complications are probably similar.[6] Among the therapeutic variables such as fluid rate and rate of fall of glucose, our study failed to identify any significant risk factors on multivariate analysis, which predisposed to the development of organ dysfunction. It would be interesting to see the relationship of inflammatory markers and their role in the development of organ dysfunction in DKA. However, since our study was retrospective, we did not have complete records of serum inflammatory markers, hence could not analyze this aspect. In addition to being retrospective, our study is limited due to its relatively small sample size. Larger prospective studies will be required to understand the risk factors and association of CE and AKI in DKA.

To conclude, a thorough search for bacterial and fungal infections is essential in every case of DKA. The severity of dehydration and acidosis appear to be common factors responsible for the development of dysfunction of both brain and kidney in DKA. Thus, it appears that the prevention of severe DKA is by far the most ideal way to prevent these complications. This emphasizes the role of early diagnosis and institution of prompt appropriate therapy for reversal in DKA.

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