

## Clinical profile of children with diabetic ketoacidosis and related cerebral edema in a tertiary care hospital from Southern Kerala

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### ABSTRACT

**Objective:** To study the clinical profile of children admitted with diabetic ketoacidosis (DKA) in the pediatric intensive care unit (PICU) of a tertiary care teaching hospital. To assess the risk factors for the development of cerebral edema in children with DKA. **Methods:** This retrospective case review was conducted in the PICU of a tertiary care teaching hospital. Details of children admitted with DKA during the period from August 2012 to November 2017 were collected with respect to clinical features, lab parameters, management, and outcome. The characteristics of children with and without cerebral edema were compared. The data were then analyzed statistically using SPSS software. **Results:** Among the 51 cases analyzed 66.7% were females and 35.3% were newly detected cases. 51.5% of the previously diagnosed and 50% of the newly detected subjects had an infection as the precipitating event. Vomiting was the most common clinical presentation (64.7%). Mean time taken for acidosis correction was 22.65 h. 12 patients (23.53%) developed cerebral edema during the course of treatment. Neurologic deterioration developed at a median of 6 h (range 1.5–36 h) after the initiation of treatment. An increased incidence of cerebral edema was found in patients who received excess fluid boluses before starting insulin treatment ( $p=0.02$ ) and newly detected cases ( $p=0.037$ ). In those who developed cerebral edema the mean blood sugar value at admission was found to be significantly higher ( $p=0.013$ ). No deaths or neurological sequelae were reported. **Conclusions:** Infections are an important precipitating factor for DKA. A significant proportion of children developed cerebral edema during treatment. New cases, excess intravenous fluid boluses, high mean blood sugar at admission, and bicarbonate administration were identified as risk factors for cerebral edema.

**Key words:** Diabetic ketoacidosis, Cerebral edema, Children, Southern Kerala

Diabetic ketoacidosis (DKA) occurs in 20–40% of children with newly diagnosed type 1 diabetes mellitus [1] and may later recur in association with illness or noncompliance with treatment. Clinically apparent cerebral edema occurs in approximately 1% of episodes of DKA in children and is associated with a mortality rate of 40–90% [2]. Cerebral edema is responsible for 50–60% of diabetes-related deaths in children [2,3]. Other causes of neurological deterioration in DKA include hypoglycemia, central nervous system (CNS) infections, and CNS hemorrhage or thrombosis, and electrolyte disturbances [4]. Even though the clinical features, management, and outcome of DKA are well described, there is a paucity of data, especially from South India. This is especially true with respect to cerebral edema associated with DKA. Early recognition of its presence and identification of risk factors for cerebral edema before the initiation of treatment and during treatment are of utmost importance for preventing morbidity and mortality. Hence, we undertook the study in a tertiary care teaching hospital in South India.

### MATERIALS AND METHODS

This retrospective case review was conducted in the pediatric intensive care unit (PICU) of a tertiary care teaching hospital during the period from August 2012 to November 2017. The study subjects included all patients with biochemically confirmed DKA [4] admitted to the PICU (Table 1). They were further classified based on the severity of acidosis [5] (Table 1). Patients having other comorbidities such as chronic kidney disease and other causes of high anion gap metabolic acidosis were excluded.

From the patient records hourly monitoring of clinical features (heart rate, respiratory rate, blood pressure, urine output, oxygen saturation, sensorium, and presence of headache and vomiting) were recorded. Details of hourly blood sugar and 4–6 hourly venous blood gas and serum electrolytes were noted. Blood urea nitrogen (BUN) and creatinine values at admission also recorded.

Hypnatremia and hyponatremia were defined as measured serum sodium level  $>150$  mmol/L and  $<135$  mmol/L, respectively. Hyperkalemia and hypokalemia were defined as serum potassium level  $>5.5$  mmol/L and  $<3.5$  mmol/L, respectively. A case of cerebral

edema was suspected when deterioration in the level of consciousness with GCS fall more than 2 was accompanied by one or more signs of raised intracranial pressure (hypertension, bradycardia, breathing pattern abnormalities, pupillary abnormalities, squint, blurred disc margins, decerebrate, or decorticate posturing). The absence of focal neurological deficits and improvement with antiedema measures were taken as a confirmation to the diagnosis of cerebral edema and to exclude other causes such as cerebral venous thrombosis and hemorrhage. Other causes of neurological deterioration such as hypoglycemia, intracranial infections, and metabolic encephalopathy were ruled out clinically and biochemically.

The treatment protocol followed was as per the standard guidelines [1,6] (Table 2).

Resolution of ketoacidosis is considered as the end of treatment of DKA. Potassium replacement was given as required as per guidelines. Antibiotics were administered whenever bacterial infection was suspected and continued in confirmed cases.

Corrected sodium and serum osmolality at admission were calculated and used for analysis [1] (Table 3).

All treatment details including details of fluids received before admission were collected. Complications which developed before and during treatment were collected with special reference to the development of cerebral edema. Time taken for correction of ketoacidosis and time interval between the initiation of treatment and diagnosis of cerebral edema noted from case records. The characteristics of children with and without cerebral edema were also compared in relation to fluids administered, blood sugar and serum osmolality at admission, blood gas, and electrolyte values to determine the risk factors for cerebral edema.

Data were statistically analyzed using SPSS version 16. Descriptive statistics were reported at baseline, with continuous

data expressed as a mean±standard deviation and categorical data expressed as counts. Children with and without cerebral edema were compared. All continuous explanatory variables were presented as means, with differences between the 2 groups compared by means of independent t-tests. Categorical explanatory variables were summarized as frequencies and percentages, with differences between the 2 groups analyzed using the Chi-square test and Fisher exact test when appropriate.  $p < 0.05$  was considered statistically significant. Permission was obtained from the Ethical Committee before conducting the study.

**RESULTS**

A total of 51 cases satisfying the criteria for DKA were analyzed. Of these 17 were males (33.3%) and 34 were females (66.7%). Male to female ratio was 1:2. Mean age was  $9.16 \pm 3.79$  years (range 1–15 years). A maximum number of cases were identified in the age group of >10 years (49%) (Table 4).

There were 18 newly detected cases (35.3%) and 33 known diabetic cases (64.7%). 3 patients had comorbidities, 2 had hypothyroidism, and 1 had congenital cytomegalovirus infection. Positive family history could be elicited in 10 patients (19.6%). Parents were affected in 2 cases and grandparents in the rest. All of them had type 2 diabetes mellitus.

Evidence of infection was noted among 26 (49%) children (Fever alone-9, acute lower respiratory infection-7, culture positive urinary tract infection-4, acute diarrheal disease-2, abscess-2, and sepsis-2). One case with sepsis had acinetobacter grown in blood culture. 51.5% of the known diabetics and 50% of the newly detected ones had an infection (Table 4). All the 7 patients with respiratory infection had clinical evidence of pneumonia characterized by localized crepitations and 4 also had radiological evidence of pneumonia. One patient had an abscess of thigh, and another had abscess of abdominal wall both of them did not have fever. 9 patients had high spiking fever without definite focus out of which 7 were CRP positive and the other 2 had persistent fever even after resolution of DKA.

Among the 51 cases, 4 had mild DKA (7.8%), 14 had moderate (27.5%), and 33(64.7%) had severe DKA. A significant proportion

**Table 1: Definition and classification of DKA**

Biochemical criteria	Classification based on severity		
	Severity	Venous pH	Bicarbonate (mmol/L)
Blood glucose >200 mg/dL	Mild	<7.3	<15
Venous pH <7.3 or bicarbonate <15 mmol/L	Moderate	<7.2	<10
Ketonuria	Severe	<7.1	<5

DKA: Diabetic ketoacidosis

**Table 2: DKA treatment protocol**

Time	Therapy
1 <sup>st</sup> h	Normal saline bolus 10 ml/kg in severely volume depleted 10–20 ml/kg in shock
2 <sup>nd</sup> h until DKA resolution	{Fluid deficit+(maintenance 2×)–bolus}/47 Insulin infusion-0.1 U/kg/h
Fluid deficit-	
Mild	50 ml/kg
Moderate to severe	85–100 ml/kg
Ketoacidosis resolution (blood pH >7.3, plasma bicarbonate >15 mmol/L)	Regular insulin at 1 U/kg/day (in 3–4 divided doses) given subcutaneously. Oral feeds started 30 min later. Insulin infusion stopped after 1 hour of subcutaneous insulin

DKA: Diabetic ketoacidosis

of children >10 years had severe DKA compared to <10 years ( $p=0.039$ ). Vomiting was the most common clinical presentation (64.7%) (Table 4). Dehydration assessed before starting fluid correction was 5% for 1 patient, 8.5% for 47 patients, and 10% for 3 patients. For one patient, the percentage of dehydration was later increased to 11% due to worsening of acidosis in between. Shock was diagnosed at admission in 9 patients (17.6%) of which 6 patients were given inotropic support also. 12 children (23.5%) received intravenous fluid boluses before hospitalization in our institution, and 14 (27.5%) had received bolus dose of insulin too before admission. Fluid received before admission was not subtracted during the calculation of fluid therapy. 28 patients (55%) received 10 ml/kg of fluid bolus, 14 (27.4%) 10–20 ml/kg, and 8 patients (15.6%) received >20 ml/kg from our hospital before starting insulin infusion. All the patients who received >20 ml/kg fluid had severe DKA, and 6 children needed inotropes also. 2 had septic shock, and the rest 4 children were weaned off inotropes in <6 h. Prolonged acidosis causing transient cardiac dysfunction may be the cause for a fluid refractory shock in them.

The biochemical parameters at admission and after 6 h are given in Table 5.

**Table 3: Corrected sodium and serum osmolality**

Measured parameter	Formula
Corrected Na	Measured serum Na+([(glucose concentration-100)÷100]×1.6)
Serum osmolality	(2×Na)+(glucose÷18)+(BUN÷2.8)

Glucose in mg/dl, serum Na in mmol/L, BUN in mg/dl and serum osmolality (mOsm/kg). BUN: Blood urea nitrogen

**Table 4: Baseline clinico-epidemiological characteristics of patients with DKA at admission**

Age in years	n (%)
1–2	4 (7.8)
2–5	5 (9.8)
5–10	17 (33.3)
>10	25 (49)
Total	51 (100)

Cases	Etiology of DKA	n (%)
Known diabetic	Missed dose	5 (9.8)
	Infection	12 (23.5)
	No identifiable cause	11 (21.6)
	Infection with missed dose	5 (9.8)
Newly detected	No identifiable cause	9 (17.6)
	Infection	9 (17.6)
	Total	51 (100)

Symptoms at admission	n (%)
Polyuria and polydipsia	15 (29.4)
Abnormal sensorium	9 (17.6)
Abdominal pain	11 (21.6)
Vomiting	33 (64.7)
Lethargy	14 (27.5)
Respiratory distress	20 (39.2)
Fever	20 (39.2)

DKA: Diabetic ketoacidosis

The mean blood sugar at admission was  $462.06\pm 88.08$  mg/dL. BUN was abnormal (>20) in 16 cases (31.4%). Mean BUN was  $19.85\pm 13.93$  mg/dL. Measured serum creatinine was abnormal in 27 (52.9%). The mean calculated serum osmolality was  $300.84\pm 11.44$  mOsm/kg.

At admission 46 patients (90.2%) had normal sodium, 4 (7.8%) had hyponatremia, and only 2 (3.9%) had hypernatremia. Maximum sodium level during treatment was also analyzed. 42 (82.3%) patients had normal sodium, 7 (13.7%) had hyponatremia, and only 2 (3.9%) had hypernatremia. A mean change in sodium level of  $8.21\pm 4.89$  mmol/l (range 1–20) was noted during treatment.

At admission 82.4% had normal potassium (K) levels, 3.9% had hypokalemia, and 13.7% had hyperkalemia. Out of the 7 patients with hyperkalemia, only 2 had serum K level >6, but electrocardiogram changes were not present. Elevated keto acids can interfere with estimation of serum creatinine and give falsely high values. But both of our patients with serum potassium >6 had a deranged BUN and serum creatinine which normalized after correction of acidosis. During treatment 18 (35.3%) developed hypokalemia (Table 6).

Maximum dose of insulin used during treatment was 0.15 U/kg/h for 4 patients. A minimum dose of 0.05 U/kg/h was needed in 5 patients. Concentration of dextrose had to be increased to 10% for 13 (25.5%) children and 12.5% for 6 children (11.8%) during the course of treatment to prevent blood glucose from falling <150 mg/dl while acidosis was persisting. 37 patients (72.5%) received fluids containing 0.9% saline only whereas 14 (27.5%) received 0.45% saline containing fluids also during correction. 3 patients received bicarbonate during treatment in view of severe acidosis.

Meantime taken for ketoacidosis correction was  $22.65\pm 14.25$  h (range 6–96 h) (Fig. 1). The 2 patients who presented with sepsis

**Table 5: Biochemical parameters**

Parameters	Mean±SD	
	At admission	6 h after starting treatment
Venous pH	7.04±0.14	7.2±0.11
Bicarbonate (mmol/L)	5.38±2.71	9.20±3.95
Partial pressure of venous CO <sub>2</sub> (mmHg)	16.36±5.24	22.64±6.25

SD: Standard deviation

**Table 6: Serum electrolyte values of children with DKA**

Parameters	Mean±SD (mmol/l)	Range
K at admission	4.67±0.72	3.0–6.4
Maximum K during treatment	4.5±0.67	3.0–6.1
Minimum K during treatment	3.63±0.63	2.2–4.9
Measured Na at admission	134.04±5.16	120–151
Corrected Na at admission	139.85±5.14	125.9–157.5
Maximum Na during treatment	140.29±5.28	132–153

DKA: Diabetic ketoacidosis, SD: Standard deviation

needed more time for correction of acidosis (96 and 36 h, respectively). In fact, the patient who needed 96 h for acidosis correction had culture positive sepsis. These patients were continuing to have high anion gap metabolic acidosis ruling out hyperchloremia as a cause of prolonged acidosis.

One patient with sepsis and DKA needed ventilatory support. Indication for ventilation was refractory shock and severe acidosis (pH 6.89 and serum bicarbonate of 1.6). This child had evidence of cerebral edema 1.5 h after starting treatment. No deaths were reported during the study period. 12 patients (23.53%) among the 51 children developed cerebral edema during the course of treatment. The diagnosis was based on the deterioration in mental status as evidenced by a fall in Glasgow Coma Scale by two or more in all the 12 patients. This was associated with bradycardia and hypertension in 8 patients, decerebrate posturing in 2 patients, and bradycardia alone in 2 patients. None of the patients had focal neurological deficits. Neurologic deterioration developed a median of 6 h (range-1.5–36 h) after the initiation of therapy for DKA (Fig. 2).

Nine patients were getting isotonic fluids during the event whereas 3 were getting half normal saline. 6 patients received mannitol as treatment, 5 received 3% saline, and 1 patient received both. None of them needed ventilation during the event, and all the patients recovered completely with antiedema measures and DKA management without any neurological sequelae. Other causes of neurological deterioration were excluded clinically and biochemically. Imaging was not done in any of our patients.

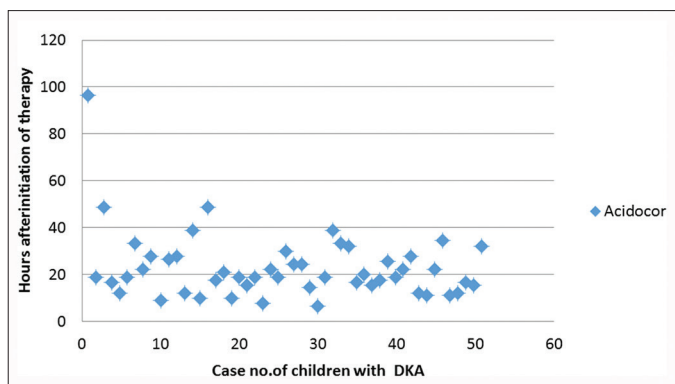


Figure 1: Time taken for correction of acidosis in children with diabetic ketoacidosis

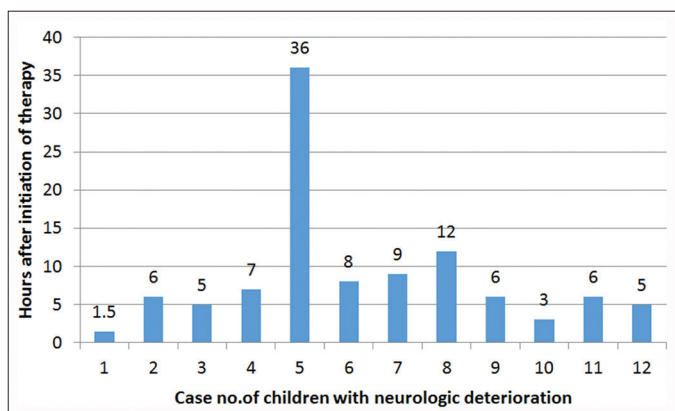


Figure 2: Time interval between the initiation of treatment and onset of cerebral edema in children with diabetic ketoacidosis

The baseline characteristics of the children with and without cerebral edema were compared.

The mean blood sugar value of the group with cerebral edema was found to be significantly higher compared to that of those without cerebral edema (Table 7) (Fig. 3).

An increased incidence of cerebral edema was noted in patients who received intravenous fluid boluses before starting treatment of DKA (p=0.02), newly detected cases (p=0.037) and those who received bicarbonate during treatment (p=0.016) (Table 8).

No difference was noted between the two groups with respect to the presence of infection, shock at presentation, and receiving insulin before starting treatment. The time taken for acidosis correction was also not different between the two groups. However, patients in the cerebral edema group showed more fluctuation in sodium level during treatment (p=0.091) (Table 9) (Fig. 4).

DISCUSSION

In this study, we analyzed 51 children diagnosed over a period of 5 years and 3 months. A definite female preponderance was noted (66.7%) with a male to female ratio of 1:2. In a study from the UK [7] females accounted for 60.5% cases whereas in a study from Srinagar, North India males were dominant (70%) [8]. In most of the studies mean age of affected children is around 7–9 years [8-10] and in our study, a mean age of 9.16 years was noted.

One important observation made by us is that 50.9% of patients had an infection as a precipitating factor. Both known diabetic cases and newly detected cases had around equal proportion (51.5% and 50%, respectively). Coexistent infection can delay acidosis correction or can even worsen acidosis. In 2 cases of sepsis with

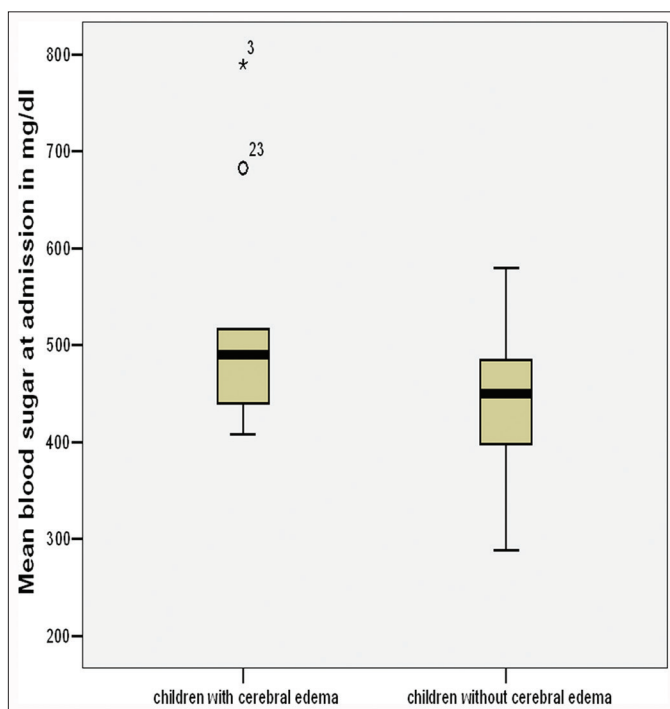
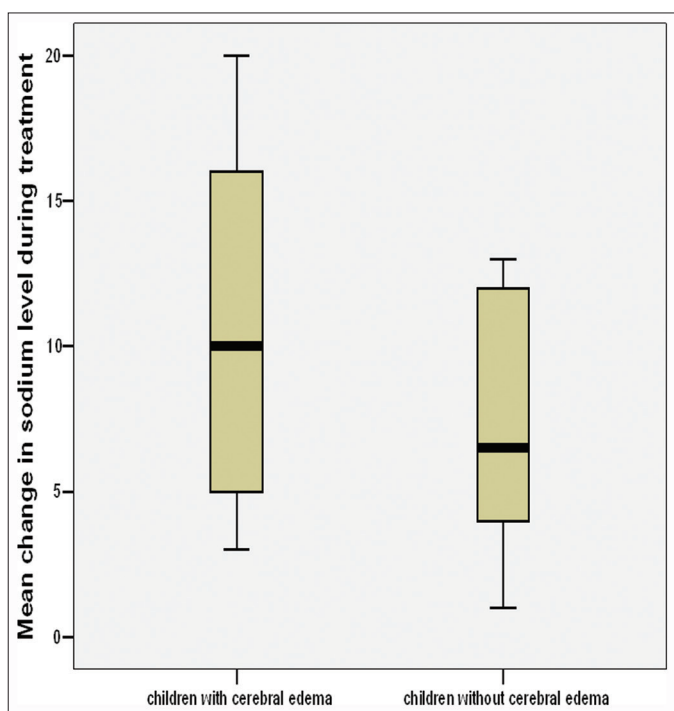


Figure 3: Mean blood sugar level at admission in children with diabetic ketoacidosis with cerebral edema and without cerebral edema

DKA in our series, the time taken for acidosis correction was 36 and 96 h against the mean value of 22.65 h. This highlights the importance of initial empirical antibiotics even if overt infection is absent especially in developing countries like ours where infection risk is high. Antibiotics may be stopped as soon as bacterial infection is ruled out. Similar to our study, a much higher rate (44%) of infection including death due to septic shock was observed in a study from North India [10]. In a study from Egypt also evidence of infection was seen in 21.9% [11].

The most common clinical presentation in our study population was vomiting followed by respiratory distress and fever. This emphasizes the importance of checking blood sugar in any sick patient presenting with similar clinical picture and also highlights the importance of proper history elicitation. In literature usually younger age shows more proportion of severe cases [12-14] whereas in our series children of >10 years age group showed



**Figure 4: Mean change in sodium level in mmol/l during treatment in children with diabetic ketoacidosis with cerebral edema and without cerebral edema**

more of severe DKA. In our study, the majority of children in whom shock was detected had severe DKA (p=0.0193) which is similar to the study from Srinagar [8].

In population studies, the mortality rate from DKA in children is 0.15–0.30% [15-17]. In a large multicenter study of DKA from the UK [2] 61 children out of 6977 hospitalization for DKA had cerebral edema (0.9%).Of the 61 children 57% recovered, 21% survived with permanent neurologic dysfunction, and 21 % died. During the study period, two other children died due to cardiac arrest associated with hypokalemia and hypocalcaemia [2]. In this study neurologic deterioration developed at a median of 7 h (range 0–25) after the initiation of therapy for DKA but in 5 %, all of whom had radiographically apparent cerebral edema it occurred before the initiation of therapy. In studies from the US also 0.5–1.5% of cerebral edema has been reported which accounts for 90% of DKA related mortality [18]. In studies from North India 13.2% cerebral edema was noted with 13.2% mortality [10]. In another study from Delhi, 14.5% of patients developed cerebral edema [19].

In our study even though a much higher rate of cerebral edema was detected (23.53%) all patients survived without neurological sequelae. Early detection and management may be the cause for 100% survival without sequelae. As all the children recovered completely within hours of neurological deterioration, cerebral venous thrombosis and hemorrhage could be excluded with reasonable certainty, and hence, imaging was not done in any of our patients. Cerebral edema may occur in the absence of acute changes in computed tomograms [20]. Unless early clinical diagnosis is made delay can lead to mortality and sequelae.

Clinically significant cerebral edema usually develops within the first 12 h after treatment has started, but can occur before treatment has begun [2,21,22] or rarely may develop as late as 24–48 h after starting treatment [1,2,23]. In our study, cerebral edema developed at a median of 6 h (range-1.5–36 h) after starting treatment. None had cerebral edema before starting treatment unlike others studies [2].

The cause of cerebral edema is controversial. Rapid fluid administration with abrupt changes in serum osmolality [24,25], hypotonic fluids, dehydration, and cerebral hypoperfusion with associated with DKA-related cerebral injury [2,26] all have been

**Table 7: Demographic and initial lab data of children with DKA with and without cerebral edema**

Variable	Mean±SD		p
	Children with cerebral edema	Children without cerebral edema	
Age (years)	9.65±3.63	9.00±3.87	0.610
Venous pH	6.99±0.12	7.05±0.15	0.182
Bicarbonate (mmol/L)	4.592±1.69	6±2.95	0.135
pCO2 (mmHg)	14.95±5.24	16.66±5.42	0.293
Blood glucose( mg/dl)	516.67±110.74 (408–790)	445.26±71.10 (289–580)	0.013 (95% CI-16.055–126.766)
BUN (mg/dl)	22.708±15.55	18.974±13.50	0.423
Calculated osmolality (mOsm/kg)	301.65±17.06	300.59±9.37	0.840
Serum Na (mmol/L)	132.42±7.53	134.5±4.31	0.216
Serum potassium (mmol/L)	4.708±0.15	4.659±0.12	0.837

BUN: Blood urea nitrogen, SD: Standard deviation, DKA: Diabetic ketoacidosis, CI: Confidence interval

**Table 8: Comparison of children with DKA with and without cerebral edema**

Variable	n (%)		P
	With cerebral edema (n=12)	Without cerebral edema (n=39)	
Female gender	10 (83.33)	24 (61.54)	0.293
Mild	0 (0)	4 (10.26)	0.254
Moderate	2 (16.67)	12 (30.77)	
Severe	10 (83.33)	23 (58.97)	
Newly detected	8 (66.67)	10 (25.65)	0.037
Treated with bicarbonate	3 (25)	0 (0)	0.011
Received IVF before admission to our hospital	6 (50)	6 (15.38)	0.022

DKA: Diabetic ketoacidosis

**Table 9: Comparison of children with DKA following treatment**

Variable	With cerebral edema (n=12)	Without cerebral edema (n=39)	p
Na level change during treatment	10.83±6.26	7.33±4.07	0.091
Time taken for Ketoacidosis correction in hours	24.92±12.44	21.95±14.84	0.533

DKA: Diabetic ketoacidosis

implicated. The factors intrinsic to DKA with probable worsening during treatment may be the cause of brain injury [27]. The degree of edema correlates with the degree of dehydration and hyperventilation at presentation [28]. Greater volumes of fluid given in the first 4 h [7,29] are also a risk factor for cerebral edema. In our study, an increased rate of cerebral edema was found in patients who received intravenous fluids boluses before starting treatment (p=0.02) which supports the literature evidence. Newly detected cases are more prone to develop cerebral edema [4,16]. A similar result is obtained in our study also (p=0.037).

All the 3 patients who received sodium bicarbonate injection during treatment developed cerebral edema (p=0.016) in our study. It is well described in literature that bicarbonate treatment is a risk factor for cerebral edema [2,4]. Controlled trials have shown no clinical benefit from bicarbonate administration [30]. Bicarbonate therapy may cause paradoxical CNS acidosis [4], and rapid correction of acidosis with bicarbonate causes hypokalemia [4,31]. Only indication for bicarbonate in DKA treatment is life-threatening hyperkalemia [4,32].

An attenuated rise in serum sodium concentration or an early fall in glucose-corrected sodium during therapy [2,29] is a risk factor for cerebral edema. Serum sodium should rise by 0.5 mmol/L for each 1mmol/L decrease in glucose concentration [4]. Steady increase in measured sodium which is ideally expected was not observed in our patient population even in patients without cerebral edema. But patients in the cerebral edema group showed more fluctuation of sodium level during treatment (Fig. 4).

Greater hypocapnia at presentation after adjusting for degree of acidosis [2,28] and more severe acidosis at presentation [7,29]

is a risk for cerebral edema. The mean values of pH, bicarbonate and pCO<sub>2</sub> were low in patients with cerebral edema in our series, even though statistical significance could not be observed. This may be due to the small sample size and absence of matching between patients with and without cerebral edema. Even though available data from other studies support the administration of insulin in the 1<sup>st</sup> hour of fluid treatment as a risk factor for cerebral edema [7] supporting evidence was not obtained in our study.

During treatment 35.3% patients developed hypokalemia in our study highlighting the importance of early potassium supplementation [4,31]. In fact, in our population in spite of potassium supplementation, this much of patients developed hypokalemia. In a study from North India, 14.5% had evidence of hypokalemia [33]. Hypokalemia is an important cause for mortality in DKA, and hence, potassium supplementation and monitoring should be emphasized.

The mean value for blood sugar was significantly higher in our study among the cases with cerebral edema. It is not described as a risk factor in other studies but is mentioned as a superimposing factor on the ischemic insult to brain which is implicated in the pathogenesis of cerebral edema [2,33,34].

This study has an inherent weakness of a retrospective study, so there could be measurement bias and issues of quality control of diagnostic tests. Also matching of study subjects could not be done. This study highlights the need for multicentric case-control studies from developing countries like India.

## CONCLUSION

Infections are an important precipitating factor for DKA. Significant proportion of children developed cerebral edema during treatment. New cases, excess intravenous fluid boluses, high mean blood sugar at admission and bicarbonate administration were identified as risk factors for cerebral edema in DKA.

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