

Factors Associated With Cerebral Edema at Admission in Indian Children with Diabetic Ketoacidosis

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Objective: To evaluate the time course and predictors of cerebral edema in diabetic ketoacidosis (DKA).

Methods: Review of hospital records of 107 episodes of DKA between January 2013 to March 2019.

Results: Cerebral edema was identified in 26 (24.3%; 22 at presentation and 4 during treatment). Cerebral edema at presentation was associated with lower (<10 mmHg) arterial carbon dioxide (OR 3.6, 95% CI 1.0,12.7; $P=0.04$), prior fluid treatment (OR 4.7, 95% CI 1.8,12.7; $P=0.001$) and new onset

diabetes (OR 3.5, 95% CI 1.1,11.1; $P=0.03$). Prior fluid was the only significant predictor on multivariate analysis ($P=0.013$). Cerebral edema resulted in a longer ICU stay [4.1 (2.3) vs 1.8 (0.9) d; $P<0.001$].

Conclusion: Cerebral edema at admission is common in Indian children with DKA and should be suspected with severe metabolic acidosis and inappropriate prior fluid treatment.

Keywords: Acidosis, Fluid therapy, Management, Outcome.

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Diabetic ketoacidosis (DKA) is the leading cause of mortality and morbidity in type 1 diabetes with cerebral edema being the major contributor [1,2]. Clinically significant cerebral edema is observed in around 2% children with DKA in Western settings with a higher prevalence in developing countries [3-6]. Timely identification and management of cerebral edema is mandatory for improving outcome of DKA. There is a paucity of Indian data regarding the same; therefore, we conducted this study to identify time course and predictors of cerebral edema in Indian children and adolescents with DKA.

METHODS

Case records of children and adolescents with DKA admitted to pediatric intensive care from January 2013 to March 2019 were reviewed after approval by the Institutional ethics committee. Information regarding clinical profile (age at admission, gender, weight and pattern of type 1 diabetes; new onset or known diabetes), precipitating factors (infection, missed insulin dose or undiagnosed type 1 diabetes), course (duration of hospital stay and insulin infusion) and time of onset of cerebral edema was collected on a predesigned proforma. Records with incomplete details were excluded.

DKA was diagnosed, classified and managed as per

International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria [7] in accordance with the hospital policy. Prior fluid volume infused was deducted from fluid calculation if precise information was available. In the absence of written documentation of fluid therapy received elsewhere, the case was managed as a new case with fluid calculation based on the present clinical condition. Monitoring of vital parameters, hourly blood glucose, 4-hourly blood ketones, blood gas and electrolyte assessment were done. Cerebral edema was diagnosed in the presence of one diagnostic, two major or one major and two minor criterion [8]. Management of cerebral edema included mannitol (20% 5 mL/kg single intravenous dose followed by 2.5 mL/kg six hourly), head-end elevation, and fluid restriction. Intubation was done only if deemed necessary by both pediatric endocrinologist and pediatric intensivist.

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Statistical analyses: Data were entered and analyzed using IBM statistical package for social sciences (SPSS version 25.0, SPSS, Inc., Chicago, IL, USA) for Macintosh. Independent sample t-test and Chi-square test were used to compare continuous and categorical variables. Parameters significant on univariate analysis were included in multivariate analysis. Logistic regression was performed to identify factors predicting

cerebral edema at admission. *P* value less than 0.05 was considered significant.

RESULTS

Out of 126 episodes of DKA admitted during the study period complete details were available for 107 [mean (SD) age, 9.0 (4.3) y; 61 boys; 66 new onset type 1 diabetes]. Fifty seven (53.3%) had severe and 22 (20.5%) moderate DKA. Cerebral edema was observed in 26 subjects (24.3%, 22 at admission and 4 during treatment). Cerebral edema at admission was diagnosed based on one diagnostic criteria (abnormal central breathing pattern) in 15 (68%), 2 major criteria in 3 (13.6%) and 1 major and 2 minor criteria in 4 (18%). Four children who developed cerebral edema during follow-up had one diagnostic criterion. Cerebral edema developed at 60 hours in a patient with refractory metabolic acidosis requiring hemodialysis and between 16-48 hours of treatment in other three patients. Cerebral edema at admission was noted in those with severe DKA than mild or moderate DKA and was associated with lower pH [6.95 (0.10) vs 7.10 (0.18); *P*<0.001], lower bicarbonate levels [5.2 (2.2) vs 8.3 (4.4) mmol/L; *P*=0.003] and higher base deficit [-25.2 (3.2) and -20.5 (6.0) mmol/L; *P*=0.001], respectively (**Table I**). There was no difference in levels of blood sugar, ketone or partial pressure of carbon dioxide in arterial blood (PaCO₂). Greater proportion of subjects with cerebral edema at admission had PaCO₂ levels below 10 mm Hg than those without it [OR (95% CI), 3.6 (1.0,12.7), *P*=0.04]. Prior fluid treatment [OR (95% CI), 4.7, (1.8,12.7) *P*=0.001] and new onset type 1 diabetes [OR (95% CI), 3.5 (1.1,11.1), *P*=0.03] increased the likelihood of cerebral edema at

admission. Prior fluid treatment was the only predictor that remained significant on multivariate regression analysis [or (95% CI), 4.5 (0.07, 0.73); *P*=0.013].

Four (4.7%) subjects developed cerebral edema [after admission [median (range) 36 (17-60) h]. Two of these developed cerebral edema at 48 and 60 hours after admission and were excluded from further analyses. The other two subjects had lower mean (SD) pH [6.9 (0.2) and 7.1 (0.2); *P*=0.07] and PaCO₂ [17.3 (9.5) and 21.2 (8.1) mm Hg; *P*=0.5] than those who did not develop cerebral edema; though statistically not significant. Seventy five percent of those with incident cerebral edema (3 out of 4) received prior fluid treatment as against 24.7% (20 out of 81) of those without cerebral edema [OR (95% CI), 9.15 (0.9, 92.9) *P*=0.027].

Treatment was associated with gradual resolution of hyperglycemia, ketosis, and acidosis after mean (SD) 7.0 (7.0), 13.5 (7.6) and 19.2 (9.4) hours, respectively. Favorable outcome was observed in 24 subjects with cerebral edema (92.3%) with mortality in two. A 14 year old girl with severe metabolic acidosis presented 2 days after receiving fluid and sodium bicarbonate at a different hospital and developed cerebral edema 16 hours after admission. During hospital stay, she developed acute kidney injury, acute respiratory distress syndrome, needed ventilation and died 5 days after admission. Second child was of a 5-year-old boy admitted with severe DKA who received prior fluid treatment and had cerebral edema at admission.

Additional interventions included ventilation in 14 and hemodialysis in two with cerebral edema. Ventilation and hemodialysis was not required in those without cerebral edema. Cerebral edema prolonged the duration of insulin infusion [35.8 (29.0) vs 16.1 (9.3) h; *P*<0.001] and ICU stay [4.1 2.3) vs 1.8 (0.9) d; *P*<0.001].

TABLE I Comparison of Children With and Without Cerebral Edema at Admission (N=107)

Parameters	Cerebral edema at admission		<i>P</i> -value
	Yes (n=22)	No (n=85)	
Age (y)	8.2 (4.4)	9.2 (4.3)	0.31
Blood Sugar (mmol/L)	29.9 (6.3)	26.3 (6.5)	0.08
*pH	6.95 (0.10)	7.10 (0.18)	<0.001
*Serum Bicarbonate (mmol/L)	5.2 (2.2)	8.3 (4.4)	0.003
*Base deficit (mmol/L)	-25.2 (3.2)	-20.5 (6.0)	0.001
Ketone (mmol/L)	5.4(0.8)	5.7 (1.0)	0.245
PaCO ₂ (mm Hg)	18.7 (7.9)	20.9 (8.1)	0.287
Sodium (mmol/L)	135.9 (6.1)	133.4 (5.9)	0.181
Potassium (mmol/L)	4.8 (0.7)	4.2 (0.9)	0.07
#New onset Type 1	18 (81.8)	48 (56.5)	0.03
#Prior fluid treatment	14 (63.6)	23 (27)	0.001

Data represented as mean (SD) or #no. (%) **P*<0.05.

DISCUSSION

Findings of the present study suggest high rate of cerebral edema at admission in Indian children and adolescents with severe DKA (38.6%). Importantly 86.4% of cerebral edema was noted at admission in contradiction to the previous reports of 22.2% [9]. This may be related to greater severity of DKA, delayed diagnosis and inappropriate fluid treatment before transfer. Prior fluid treatment was the only factor predicting cerebral edema at admission in accordance with previous studies [10]. High index of suspicion for cerebral edema in those with severe DKA and prior fluid treatment is therefore essential. Lower PaCO₂ levels predicted cerebral edema at admission, as seen in previous studies [11,12].

The rate of incident cerebral edema (4.7%) in our

What This Study Adds?

- Cerebral edema is common at admission in Indian children and is frequently associated with inappropriate prior fluid treatment.

study is similar to Western reports in subjects with DKA of similar severity, suggesting similar risk profile. Recent studies have indicated a baseline rate of cerebral edema irrespective of rate of fluid administration or solute concentration [13,14]. Inclusion of greater proportion of subjects with milder DKA may limit their generalizability in Indian setting [14]. This has been attributed to intrinsic characteristic of DKA and not the effect of treatment [15]. All subjects with incident cerebral edema in our study had severe DKA (undetectable serum bicarbonate and pH below 7.0) highlighting the need for high index of suspicion in this setting. The present study suggests favorable outcome of DKA related cerebral edema with uneventful recovery in over 90% despite the need for ventilation in half. Moreover, the mortality in this study was unrelated to cerebral edema (renal failure in one and ARDS in other). This reflects the effects of close clinical observation, timely identification and treatment.

Cerebral edema imposes significant morbidity and mortality in DKA as reflected by doubling in duration of insulin infusion and intensive care stay. This is similar to previous observation of cerebral edema associated increased hospital stay and highlights the need for prevention of cerebral edema by early diagnosis and timely referral of DKA [16].

Retrospective design is a limitation of our study; protocolized management by the same clinical leads over however, the study period and close documentation ensured uniformity of treatment and availability of data. Lack of precise information regarding the amount and type of fluid administered before admission is a limitation but reflects real life circumstances where these details are usually not available. The diagnosis of cerebral edema was established on clinical grounds and not confirmed radiologically. However, this represents the standard of clinical care as diagnosis of cerebral edema is largely clinical and delay in treatment for radiological confirmation can be lethal. Robust clinical criteria assessed by two pediatricians and response to mannitol substantiate our diagnosis.

This study has significant implications for DKA management in resource-poor settings receiving sick patients with unclear prior treatment. It emphasizes the need of specifying the amount and type of fluid therapy

by referring physicians and suggests the key role of primary (prevention of DKA by early diagnosis), secondary (timely detection and treatment of DKA) and tertiary prevention (high index of suspicion for cerebral edema and urgent management) in limiting DKA, related morbidity and mortality.

Contribution: NA,CD,RP: involved in patient management and data collection; NA: literature review, statistical analysis and drafted the initial manuscript; RK,RS,AB: involved in patient care; AB: conceptualized and planned the study, conducted statistical analysis, critically reviewed the manuscript and would act as guarantor of the paper.

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