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The incidence of cerebral edema in pediatric patients with diabetic ketoacidosis: a retrospective study

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Abstract

Objective Cerebral edema is a severe and potentially fatal complication of diabetic ketoacidosis (DKA), particularly in pediatric patients. Despite its clinical significance, limited data exist on its incidence and associated risk factors in resource-limited settings. This study aimed to determine the incidence of cerebral edema in pediatric patients with DKA and investigate potential contributing factors. This retrospective study analyzed data from 270 pediatric DKA patients admitted to the Children's Medical Center Hospital, Tehran, between March 2018 and March 2020. Patients aged 1 day to 18 years were included based on standard DKA diagnostic criteria (blood glucose > 250 mg/dL, pH < 7.3, bicarbonate < 18 mEq/L, and ketonemia/ketonuria). Patients with incomplete records or pre-existing neurological conditions were excluded. The statistical analyses included independent t-tests and Fisher's exact tests.

Results The incidence of cerebral edema was 6.67%. Elevated blood glucose levels at admission were significantly associated with cerebral edema ($P = 0.01$), suggesting a potential role in its pathophysiology. Additionally, a strong correlation was observed between cerebral edema and ICU admission ($P < 0.001$), indicating a more severe disease course. The results suggest that early glucose control and neurological monitoring are critical for preventing adverse outcomes such as cerebral edema in pediatric DKA patients.

Keywords Diabetic ketoacidosis, Cerebral edema, Pediatric, Hyperglycemia

Introduction

Diabetic ketoacidosis (DKA) is a serious, potentially life-threatening acute complication of diabetes mellitus, primarily affecting individuals with type 1 diabetes [1]. The pathophysiology of DKA involves complex metabolic derangements that, if untreated, can result in significant morbidity and mortality. It is characterized by hyperglycemia, metabolic acidosis, and ketosis, which arises from an absolute or relative deficiency of insulin [2, 3]. This deficiency triggers lipolysis, followed by ketogenesis, resulting in the accumulation of acidic ketone bodies in the blood [4]. In the pediatric population, DKA presents unique challenges, as children are more susceptible to severe complications due to their physiological and developmental differences compared to adults [5]. In children, DKA frequently occurs as the initial presentation of type 1 diabetes, which underscores the critical need for early diagnosis and intervention to prevent severe complications and reduce mortality rates [6].

The prevalence of DKA at the onset of diabetes ranges from 30 to 40% [7]. A retrospective study conducted

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between 2002 and 2012 in British Columbia, Canada, revealed that 32.4% of incident cases of type 1 diabetes experienced episodes of DKA at the time of diagnosis [8]. The global prevalence of DKA is increasing worldwide. A systematic review revealed that the prevalence of DKA among youth with type 1 diabetes increased from 35.3% in 2010 to 40.6% in 2016 [9], which highlights the need for identifying contributing factors and implementing targeted interventions to reduce the incidence of DKA.

DKA can result in mortality if prompt and appropriate management is not initiated [10]. Before the advent of insulin therapy, DKA was associated with an almost 100% mortality rate. However, advancements in treatment have significantly reduced mortality rates, which are now substantially lower. Currently, the overall mortality rate in children with DKA ranges from 0.15 to 0.35% in developed countries and from 3.4 to 13.4% in developing countries [11]. The results of a study conducted in Ethiopia revealed that the overall mortality rate among children with DKA was 10.6 per 1000 person-days of observation [12]. Another study conducted in Kenya reported a mortality rate of 6.9% among pediatric patients with DKA [13]. In another study conducted in Turkey, the mortality rate was reported to be low at 0.87% [14]. The variation in mortality rates across regions underscores the need for further research, especially in resource-limited settings.

The complications of DKA are multifaceted and can have both immediate and long-term effects on pediatric health [15]. Electrolyte imbalances, including hypokalemia, hyperkalemia, hyponatremia, and hypophosphatemia, are nearly universal in DKA and contribute to cardiac arrhythmias, muscle weakness, and other systemic effects [16, 17]. Acute kidney injury, another common complication, arises due to severe dehydration and reduced renal perfusion, further complicating fluid and metabolic management [18]. Among the acute complications of DKA, cerebral edema is the most severe and potentially fatal, with a mortality rate ranging from 20 to 40%. It occurs in up to 1% of pediatric DKA cases, particularly in individuals under 20 years of age [19]. The condition results from rapid osmolar shifts and inflammatory processes during treatment, leading to brain swelling that can cause irreversible neurological damage or death if not promptly managed [20].

While significant progress has been made in understanding DKA and its complications, notable gaps remain in the literature. Notably, few studies have assessed the complications of DKA, particularly cerebral edema, in pediatric patients in Iran, a resource-limited country. This lack of data hinders the development of targeted interventions and the improvement of outcomes in this population. This issue highlights the need for region-specific research to address these gaps. This study aimed to address these gaps by analyzing cerebral edema associated with DKA in pediatric patients using retrospective data.

Materials and methods

This retrospective study was conducted at the Children's Medical Center Hospital, affiliated with Tehran University of Medical Sciences, a major referral center admitting pediatric patients from all regions of Iran. Selecting this hospital as the research setting ensures the inclusion of patients from diverse geographical areas, which enhances the generalizability of the findings.

The study included all pediatric patients aged 1 day to 18 years who were referred to the Children's Medical Center Hospital with a diagnosis of DKA between March 21, 2018, and March 20, 2020. The criteria for DKA diagnosis included blood glucose levels above 250 mg/dL, blood pH less than 7.3, serum bicarbonate levels less than 18 mEq/L, and the presence of ketonuria or ketonemia [21]. A total of 270 patients were eligible for inclusion. Exclusion criteria were applied to ensure data quality and focus, including patients with incomplete medical records relevant to the study variables, those with underlying neurological conditions that could confound the assessment of cerebral edema, or patients who developed cerebral edema prior to hospital admission. These criteria ensured the study focused on cerebral edema arising specifically during the course of DKA management. None of the 270 eligible patients met the exclusion criteria, and all were included in the final analysis.

Data were collected retrospectively and included demographic information (age and gender), clinical variables (blood glucose levels at admission), cause of DKA (e.g., non-adherence to insulin therapy, viral infection, underlying disease, antibodies against insulin, insulin resistance), frequency of recurrence, and whether the patient required ICU admission. Cerebral edema was confirmed in cases that presented clinical findings suggestive of the condition, such as changes in consciousness level, diagnostic imaging like brain CT scans, and final confirmation by a neurologist.

The collected data were analyzed using SPSS software version 16. Descriptive statistics were employed to summarize the data, with continuous variables presented as means and standard deviations, and categorical variables reported as frequencies and percentages. To examine associations between variables and outcomes, inferential statistical tests were applied. Independent t-test was used to compare the means of continuous variables between groups, while the Fisher's exact test was used to assess associations between categorical variables and specific outcomes. A P-value of less than 0.05 was considered statistically significant for all analyses.

Table 1 The characteristics of patients and their association with the incidence of cerebral edema

Variable	Mean ± SD	Incidence of Cerebral Edema
Age (Year)	8.95 ± 3.95	0.38*
Blood glucose levels at admission (mg/dL)	410.74 ± 127.61	0.01*
	N (%)	
Gender		0.51**
Male	129 (47.8%)	
Female	141 (52.2%)	
Cause of DKA		0.92**
Non-adherence to insulin therapy	151 (55.9%)	
Viral infection	84 (31.1%)	
Underlying disease	30 (10.8%)	
Antibodies against insulin	3 (1.1%)	
Insulin resistance	2 (0.7%)	
First recurrence		0.19**
Yes	228 (84.4%)	
No	42 (15.6%)	
Admission in ICU		< 0.001**
Yes	102	
No	168	

*Independent t-test **Fisher's exact test

Results

The study included 270 pediatric patients diagnosed with DKA. The mean age of the patients was 8.95 ± 3.95 years, with 47.8% being male and 52.2% female. Among the cohort, the leading cause of DKA was non-adherence to insulin therapy (55.9%), followed by viral infections (31.1%) and underlying diseases (10.8%). Less common causes included antibodies against insulin (1.1%) and insulin resistance (0.7%). The mean blood glucose level at admission was 410.74 ± 127.61 mg/dL. Cerebral edema was diagnosed in 18 cases, resulting in an incidence rate of 6.67% among DKA patients. There were no statistically significant associations between the incidence of cerebral edema and gender ($P = 0.51$), the cause of DKA ($P = 0.92$), or whether it was the patient's first recurrence of DKA ($P = 0.19$). However, elevated blood glucose levels at admission were significantly associated with the development of cerebral edema ($P = 0.01$). A significant correlation was observed between the incidence of cerebral edema and ICU admission ($P < 0.001$) (Table 1).

Discussion

This study investigated the incidence of cerebral edema in pediatric patients with DKA, revealing an incidence rate of 6.67%. In comparison, a study conducted in Argentina on adult patients reported a prevalence of cerebral edema among DKA patients of 1.44%, which is notably lower than the incidence observed in our study [22]. Additionally, experts have traditionally estimated that cerebral edema develops in up to 1% of pediatric DKA cases [19], which contrasts with our findings. The higher incidence rate observed in this study may be attributed to differences in study populations and diagnostic criteria. Another possible explanation is the delayed presentation of DKA or a delay in referring patients to a healthcare setting, leading to prolonged hyperglycemia and greater osmotic imbalances, which could contribute to this discrepancy. These findings highlight the importance of early recognition and careful management of DKA to minimize the risk of cerebral edema.

The results revelad a significant association between cerebral edema and elevated blood glucose levels at admission. Severe hyperglycemia leads to significant osmotic shifts, and rapid glucose reduction during treatment can cause a sudden drop in plasma osmolality, driving water into brain cells and increasing the risk of cerebral swelling [19, 23]. Additionally, high blood glucose at admission indicates prolonged hyperglycemia, suggesting delayed presentation and more severe dehydration, which make the brain more vulnerable to fluid shifts during resuscitation. Furthermore, high blood glucose is associated with cerebral edema due to its effects on the blood-brain barrier (BBB) and vascular permeability. Hyperglycemia, along with ketoacidosis, cerebral hypoxia, and inflammation, disrupts osmotic balance and increases endothelial permeability. As a result, the BBB becomes less restrictive to insulin, sodium, and water, promoting fluid shifts into brain tissue and accelerating the development of cerebral edema [24]. Consistent with our findings, previous case report studies have identified high blood glucose at admission as a potential risk factor for cerebral edema in patients with DKA [19, 25]. Supporting our results, a review study by Jafari et al. (2022) provided evidence of a potential relationship between high blood glucose at admission and the incidence of cerebral edema in pediatric DKA patients [26].

Another notable finding was the strong correlation between cerebral edema and ICU admission. Patients requiring ICU care for DKA are often those presenting with more severe metabolic derangements, profound dehydration, and altered mental status, all of which are recognized risk factors for cerebral edema. This finding is consistent with the study by Patel et al. (2016), which reported that DKA patients with cerebral edema have a longer length of stay and higher hospitalization costs [27].

The observed incidence of cerebral edema, combined with its association with high blood glucose levels and ICU admission, underscores the importance of early identification and preventive strategies in managing pediatric DKA. Given the life-threatening nature of this complication, routine monitoring of neurological status,

careful fluid management, and gradual correction of hyperglycemia are essential components of treatment. Future research should focus on identifying early biomarkers that could aid in the timely detection of DKA and cerebral edema, ultimately improving outcomes in this vulnerable population.

Limitations

One of the key strengths of this study is its relatively large sample size and the inclusion of data from a major referral center, which enhances the generalizability of the findings. Additionally, the study provides valuable insights into the incidence of cerebral edema in pediatric DKA patients, a critical but understudied complication in resource-limited settings. The rigorous methodology, including strict diagnostic criteria and statistical analysis, strengthens the validity of the results. However, this study also has several limitations. As a retrospective study, it is subject to potential biases, including missing data and reliance on medical records for diagnosis and clinical variables. Additionally, the study did not assess long-term neurological outcomes in affected patients, limiting its ability to evaluate the full impact of cerebral edema in pediatric DKA cases. Future prospective studies with standardized diagnostic protocols and follow-up assessments are recommended to address these limitations. Furthermore, we recommend that future research also focus on optimizing the management of diabetic ketoacidosis, including the role of fluid resuscitation strategies and preventive measures for cerebral edema. Additionally, incorporating advanced techniques such as deep learning models in future research could provide valuable insights for predicting the risk factors of cerebral edema in pediatric DKA patients.

Conclusion

This study found that the incidence of cerebral edema in pediatric DKA patients was 6.67%, higher than previously reported estimates. Elevated blood glucose levels at admission were significantly associated with an increased risk of cerebral edema, likely due to osmotic shifts, blood-brain barrier dysfunction, and delayed presentation. Additionally, cerebral edema was correlated with ICU admission, underscoring its severity and impact on patient outcomes. These findings highlight the importance of early recognition, careful management of hyperglycemia, and close monitoring of neurological status in pediatric DKA patients. Future research should focus on identifying early biomarkers and optimizing treatment protocols to reduce the risk of cerebral edema and improve outcomes in this vulnerable population.

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Author contributions
S.M: Study design, data analysis, data interpretation, and drafting; B.G: Study design, data analysis, data interpretation, and drafting; M.M.R: Study design, data analysis, data interpretation, and drafting; A.Z: Study design, data analysis, data interpretation, and drafting; All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Data availability
The data generated and analyzed during the current study is not publicly available to ensure data confidentiality but is available from the corresponding author on reasonable request and with the consent of the research participants.

Declarations

Ethics approval and consent to participate
Ethical approval for this study was obtained from the Ethics Committee of Tehran University of Medical Sciences (Approval No. IR.TUMS.CHMC.REC.1399.035). The research was conducted in compliance with the ethical guidelines set forth in the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent to participate was not obtained from the participants. The need for informed consent was waived by the Ethics Committee, as the study involved the use of anonymized patient data collected as part of routine clinical care, with no identifying information recorded. All patient data were anonymized to maintain confidentiality.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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