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The Incidence of Cerebral Edema in Pediatric Diabetic Ketoacidosis

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ABSTRACT

Introduction: Cerebral edema is an uncommon but devastating consequence of diabetic ketoacidosis occurring more in children than adults. Younger children and those with newly diagnosed diabetes are at highest risk. The objective of this study is to determine the frequency of cerebral edema in pediatric diabetic ketoacidosis at Children's Hospital, Lahore in children with type 1 diabetes mellitus.

Methods: This descriptive study was carried out in the pediatric intensive care units and medical wards of the Children's Hospital and the institute of Child Health, Lahore from 2nd Feb 2016 to 2nd Aug 2016. A total of 150 patients fulfilling the inclusion criteria were enrolled. After taking consent from parents, demographic information including name, age, sex, address, and date of admission were recorded. Fundoscopic findings were recorded before initiating diabetic ketoacidosis treatment and neurological examination was conducted at presentation. Cerebral edema was labeled as per operational definition and sampling was done as per hospital DKA management protocol.

Results: In our study, out of 150 cases, 58.67%(n=88) were between 1-7 years of age while 41.33%(n=62) were between 8-14 years of age, mean + sd was calculated as 6.92+3.12 years, 51.33%(n=77) were male and 48.67%(n=73) were females. Frequency of cerebral edema in pediatric diabetic ketoacidosis at children's hospital Lahore in the child with type 1 diabetes mellitus was calculated in 18.67%(n=28) while 81.33%(n=122) had no findings of cerebral edema.

Conclusions: Frequency of cerebral edema is high in pediatric diabetic ketoacidosis at Children's Hospital Lahore in the child with type 1 diabetes mellitus.

INTRODUCTION

Diabetic ketoacidosis (DKA) is a metabolic derangement characterized by the triad of hyperglycemia, acidosis and ketosis that occurs in the presence of very low levels of effective insulin action. It is the leading cause of mortality in children with diabetes and is associated with increased morbidity and healthcare expenditure.[1,2] Worldwide, approximately 65,000 children <15 years of age develop Diabetes Mellitus(DM) each year and up to 80% of these present with DKA.[3]

Cerebral edema (CE) is one of the potentially devastating neurological complications of DKA. The incidence of clinically apparent cerebral edema is 0.9%, with a mortality of 22% and 29% of survivors suffer neurological sequelae. Literatures from developed countries show the incidence of cerebral edema to be 0.1-5% while the limited data from developing countries reveal a higher rate of up to 29%.[4] The objective of this study was

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to determine the frequency of cerebral edema in pediatric diabetic ketoacidosis at Children's Hospital Lahore in the child with type 1 diabetes mellitus.

METHODS

This was a prospective hospital based descriptive study, conducted at The Children's Hospital Lahore from February 2016 to August 2016. Children less than 14 years of age admitted with a diagnosis of DKA at the pediatric intensive care unit (PICU) and general medical ward were included. This study was conducted as a part of dissertation after obtaining permission from the Institutional Review Board.

Inclusion Criteria

- Patients of either gender up to 14 years presenting in DKA (as per operational definition).
- Patients of DM-1 diagnosed at least 6 months ago (as per operational definition).

Exclusion Criteria

- Patients with previous neurological deficit (assessed clinically by the attending doctor).

Operational definition

Diabetic ketoacidosis

- **Diabetic ketoacidosis (DKA):** is defined as a venous pH<7.3 seurm bicarbonate concentration <15 mmol/L, blood glucose concentration >20 mg/dL (11 mmol/L) and Ketonuria (++)
- **Type 1 DM (Diabetes Mellitus):** fasting plasma glucose ≥ 126mg/dl. On 2 separate occasions apart, patients diagnosed at least 6 months age were included.
- **Cerebral Edema:** was assessed by Neurological state criteria[5] and presence of Papilledema during funduscopic. Funduscopic findings were graded as I-V after each examination Grade I-V after each examination. (Grade I or higher until be labeled as papilledema). A method of clinical diagnosis based on bedside evaluation of neurological state.

Neurological State Criteria

Diagnostic Criteria

- Abnormal motor or verbal response to pain.
- Decorticate or decerebrate posture.
- Cranial Nerve palsy(especially III,IV and VI)
- Abnormal neurogenic respiratory pattern.

Major Criteria

- Altered mentation/Fluctuating level of consciousness (GCS<14)
- Sustained rate of deceleration (decrease more than 20 beats/min)not attributable to improved intravascular volume or sleep)
- Age-inappropriate incontinence.

Minor Criteria

- Vomiting
- Headache
- Lethargy or not easily arousable
- Diastolic blood pressure>90mm of Hg.
- Age<5 years

Cerebral edema diagnosed if one diagnostic criteria or two major criteria Or 1 major and 2 minor criteria.

Modified Frisen Scale for Papilledema Grading

Grade	Definition/Findings
0	Normal optic disk
I	Minimal papilledema: subtle C-shaped halo of disk edema with a normal temporal disk margin
II	Low-degree papilledema: circumferential halo of disk edema
III	Moderate papilledema: obscuration of one or more segments of the major blood vessels leaving the disk
IV	Marked papilledema: partial obscuration of a segment of major blood vessel on the disk.
V	Severe papilledema: partial or total obscuration of all blood vessels on the disk

Data collection procedure

A total of 150 patients admitted in the hospital fulfilling the inclusion criteria were enrolled in the study. After taking Informed consent from parents and their demographic information including name, age, sex, address, date of admission will be recorded. Data including funduscopic recorded before initiating DKA treatment. Neurological status examination was conducted at presentation. Cerebral edema was labelled as per operational definition. Sampling was done as per hospital DKA management protocol and no additional sampling was performed.

Sample size and selection: Sample size was 150, calculated with 95% confidence level, 6% margin of error and taking expected percentage of cerebral edema i.e. 13% in pediatric diabetic ketoacidosis in children with type-I diabetes mellitus. Non probability, consecutive sampling was done.

Data analysis: SPSS (version 17) software was used to analyze the data. Quantitative variable like age was described as mean ± sd. Categorical variables like gender and presence or absence of cerebral edema were described as frequencies and percentages. The data was stratified for age, gender, duration of diabetes mellitus (DM) to deal with effect modifiers. Post stratification chi square test was applied. P value <0.05 was considered as significant.

RESULTS

A total of 150 cases fulfilling the inclusion criteria were enrolled to determine the frequency of cerebral edema in paediatric diabetic ketoacidosis at Children's Hospital Lahore in the child with type 1 diabetes mellitus. Patients were distributed as 58.67 %(n=88) were between 1-7 years of age while 41.33 %(n=62) were between 8-14 years of age, mean±sd was calculated as 6.92±3.12 years. (Table No. 1) Gender distribution shows that 51.33 %(n=77) were male and 48.67 %(n=73) were females (Table No. 2). Frequency of cerebral edema in pediatric diabetic ketoacidosis at children's hospital Lahore in the child with type 1 diabetes mellitus was calculated in 18.67%(n=28) while 81.33%(n=122) had no findings of cerebral edema(Table No. 3). The data was stratified for age, gender, duration of DM to deal with effect modifiers. Post stratification chi square test was applied. P value <0.05 was considered as significant (Table No. 4 & 5)

Table 1: Age distribution (n=150)

Age(in years)	No. of patients	%
1-7	88	58.67
8-14	62	41.33
Total	150	100
Mean±SD	6.92±3.12	

Table 2: Gender distribution (n=150)

Gender	No. of patients	%
Male	77	51.33
Female	73	48.67
Total	150	100

Table 3: Frequency of cerebral edema in pediatric diabetic ketoacidosis at Children's hospital Lahore in children with type 1 diabetes mellitus (n=150)

Cerebral edema	No. of patients	%
Yes	28	18.67
No	122	81.33
Total	150	100

Table 4: Stratification for frequency of cerebral edema in pediatric diabetic ketoacidosis at Children's hospital Lahore in children with type 1 diabetes mellitus with regards to age (n=150)

Age (in years)	Cerebral edema		P value
	Yes	No	
1-7	15	73	0.54
8-14	13	49	

Table 5: Stratification for frequency of cerebral edema in pediatric diabetic ketoacidosis at Children's hospital Lahore in children with type 1 diabetes mellitus with regards to gender(n=150)

Gender	Cerebral edema		P value
	Yes	No	
Male	11	66	0.15
Female	17	56	

Table 6: Stratification for frequency of cerebral edema in pediatric diabetic ketoacidosis at children's hospital lahore in the child with type 1 diabetes mellitus with regards to duration of diabetes mellitus

(n=150

Duration of diabetes mellitus	Cerebral edema		P value
	Yes	No	
1-3 years	10	96	0.000
>3 years	18	26	

DISCUSSION

Cerebral edema (or cerebral injury) is an uncommon but potentially devastating consequence of diabetic ketoacidosis (DKA). It is far more common among children with DKA than among adults. Young children and those with newly diagnosed diabetes are at highest risk. Symptoms typically emerge during treatment for DKA, but may be present prior to initiation of therapy. Overall mortality rates for diabetic ketoacidosis (DKA) in children and adolescents range from 0.15 to 0.51 percent in national population studies in Canada, the United Kingdom, and the United States,[6] 50 to 80

percent of diabetes-related deaths are caused by cerebral edema. Other causes of death from DKA include aspiration pneumonia, multiple organ failure, gastric perforation, and traumatic hydrothorax.[6]
We planned this study with the view that in particular, there are few studies available that have looked at the clinical profile and outcomes of DKA in the pediatric age group in Pakistan, but no local study on cerebral edema in DKA children.

In our study, out of 150 cases, 58.67%(n=88) were between 1-7 years of age while 41.33%(n=62) were between 8-14 years of age, mean ± SD was calculated as 6.92±3.12 years, 51.33%(n=77) were male and 48.67%(n=73) were females, frequency of cerebral edema in pediatric diabetic ketoacidosis at children's hospital Lahore in the child with type 1 diabetes mellitus was calculated in 18.67%(n=28) while 81.33%(n=122) had no findings of cerebral edema.

It has been hypothesized that cerebral edema in children with diabetic ketoacidosis may be caused by the accumulation of osmolytes in brain cells exposed to hyperosmolar conditions. A rapid decrease in extracellular osmolality during treatment would then result in osmotically mediated swelling of the brain.[7] Although osmotic factors and other mechanisms may play a part in the development of cerebral edema, our data lend support to the hypothesis that cerebral edema in children with diabetic ketoacidosis is related to brain ischemia.[7] Both hypocapnia, which causes cerebral vasoconstriction, and extreme dehydration would be expected to decrease perfusion of the brain. In addition, bicarbonate therapy causes central nervous system hypoxia in laboratory animals with diabetic ketoacidosis.[8] Subclinical brain swelling, as detected by ventricular narrowing on a computed tomography (CT) scan, has been reported in the majority of children with DKA in some studies, while others reported much smaller proportions. All of these studies were limited by small numbers and lack of appropriate control groups. Cerebral edema is most likely to occur between 4 and 12 hours after the initiation of therapy, but may occur any time within the first 24 hours. Rarely, cerebral edema has developed prior to initiation of therapy or after the first 24 hours. Thus, therapy may exacerbate but not initiate the pathologic process leading to cerebral edema.[9]

In a study of 41 children with DKA, the intercaudate width of the frontal horns of the lateral ventricles was measured by magnetic resonance imaging (MRI).[8] The lateral ventricles were significantly smaller in patients during treatment for DKA than after recovery (mean width 9.3 ± 0.3 versus 10.2 ± 0.3 mm, respectively). Fifty-six percent of the children had ventricular narrowing during treatment, and these children were more likely to have mental status changes than those without narrowed ventricles (Glasgow coma scale [GCS] scores below 15 occurred in 12 of 22 with ventricular narrowing, versus 4 of 19 without).

Despite the lack of a control group, these findings suggest that cerebral swelling occurs commonly in children with DKA. However, it remains unclear whether subclinical brain swelling noted in this study is a precursor to clinically significant cerebral edema and if so, what factors determine progression. Similar changes in mental status have been reported among children with other causes of acidosis, so it is difficult to determine whether the observed mental status changes in this study are due to the cerebral edema or to the underlying acidosis.[10] Previously, Lawerence et al found incidence to be 0.5% in Canada and petal et al[9] found it to be 0.64% in U.S.A. but the incidence of CE in developing country is high.[5] Jayashree et al found 13% cerebral edema in Pediatric DKA. Cerebral edema was reported in 26% in one series.[3] Cerebral edema was found in 23% by Varadarajan et al.[11] Clinically significant cerebral edema usually develops within the first 12 h after treatment has started, but can occur before treatment has begun.[4]

Kanwal SK and others studied the clinical profile of the Indian children admitted with DKA and recorded that the mean age of patients at presentation was 7.4±3.9 y; 27 boys and 28 girls were enrolled[11] Hypernatremia, hypokalemia, cerebral edema and renal failure were observed in 20%, 14.5%, 14.5% and 7.2% , respectively. While 12.72% had fatal outcome, cerebral edema with or without renal failure and sepsis accounted for most of the deaths. Edge, et al studied sex, age, or whether diabetes was new or previously diagnosed in relation to CE. Study revealed younger patients may be at greater risk for CE. Newly diagnosed diabetes was associated with about three times the risk of cerebral edema compared with previously diagnosed diabetes.[12]

Previous investigations of cerebral edema in children with diabetic ketoacidosis cited younger age, a new diagnosis of diabetes, and the rate of fluid administration as factors associated with cerebral edema. In these studies, however, children with cerebral edema were not compared with controls, and there was no adjustment for possible confounding factors, as in our study which are the major limitations to the study.

In our study, we have reported the frequency but the correlation of timing of edema with the onset of DKA is not done.

CONCLUSIONS

We concluded that the frequency of cerebral edema is high in pediatric diabetic ketoacidosis at Children's Hospital Lahore in the child with type 1 diabetes mellitus. However association of cerebral edema with the stages of DKA could not be commented and needs further analytical studies.

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