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ORIGINAL ARTICLE

Risk Factors of Cerebral Edema in Diabetic Ketoacidosis admitted in PICU of a Tertiary Care Hospital

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ABSTRACT

Objective: To determine the risk factors for development of cerebral edema in children with Diabetic Ketoacidosis (DKA).

Study Design: An observational study.

Place and Duration of Study: Pediatric Critical Care Unit of The Children's Hospital and the Institute of Child Health, Lahore from February 2015 to December 2018.

Material and Methods: An observational study conducted at Pediatric Critical Care Unit of the Children's Hospital and the Institute of Child Health, Lahore in children up to the age of 16 years with T1DM who presented with DKA from February 2015 to December 2018. Data analysis was done by SPSS. Statistical significance was analyzed and chi square test was applied for categorical variables and p value <0.05 was considered significant.

Results: A total of 152 patients with DKA were included having mean age of 7.86 ± 4.06 years. Majority of cases 89 (59%) were of new onset diabetes. The factors associated with increased relative risk of cerebral edema were unconsciousness at presentation (OR: 5.470; 95% CI: 2.822-10.603) (p=<0.001), initial treatment at periphery/local hospital (OR: 2.420; 95% CI: 1.449-4.042) (p=0.001), severe metabolic acidosis (OR: 11.370; 95% CI: 1.624-79.586) (p=<0.001), hypernatremia (p=<0.001) and hypokalemia (p=0.02).

Conclusion: Unconsciousness at presentation, initial treatment at periphery/local hospital, severe metabolic acidosis, hypernatremia and hypokalemia were most common risk factors identified for development of cerebral edema.

Key Words: *Type 1 diabetes mellitus, Diabetic ketoacidosis, Cerebral edema, Children, Risk factors*

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases in childhood, resulting from insulin deficiency, caused by autoimmune destruction of the insulin-producing pancreatic beta cells.[1] Environmental factors and genetic predisposition triggers autoimmune destruction of the beta cells.[2] There is a decrease in insulin or an ineffective circulating insulin level resulting in elevations of counter regulatory hormone, ultimately causing diabetic ketoacidosis (DKA) in T1DM. Generally, the most common presentation is in childhood, but one-fourth of cases often have delayed presentation and they

are diagnosed in adulthood. Globally an overall increase in the disease burden is noted over the years and countries in Europe has the highest incidence (76%) and countries in Sub-Saharan Africa has lowest (8%).[2,3]

DKA is a common manifestation of T1DM causing significant morbidity and mortality.[4] It is diagnosed by a characteristic biochemical triad of hyperglycemia ketonemia (ketonuria) and acidemia. International Society for Pediatric and Adolescent Diabetes defines DKA as random blood glucose level >200 mg/dl, pH <7.3, bicarbonate <15 mmol/L, ketonemia, and ketonuria.[5] Understanding about the factors associated with DKA at diagnosis and to obviate the delay in diagnosis and its management is therefore imperative.[5] Mortality in T1DM is generally attributed to cerebral edema, severe infection, pulmonary edema, hypokalemia or cardiac arrhythmias.[6]

Cerebral edema ranging from mild to severe may occur in children presenting with DKA.[7] Cerebral edema is rare but one of the potentially fatal complications of DKA, most commonly affecting children in the younger age group. All children with T1DM irrespective of the age of the child presenting with DKA should be monitored carefully for the development of cerebral edema. Published data from developed countries have shown a lower incidence of cerebral edema (0.1-5%), while from developing countries although the limited data is available, it revealed a higher rate of up to 29%. To prevent cerebral edema in DKA the therapeutic guidelines are slow rehydration, avoidance of hypotonicity and avoiding unnecessary bicarbonate therapy.[7] Due to high incidence of cerebral edema, risk factors need to be studied especially in developing countries. Further, there are peculiarities with our health system from basic to tertiary level that may contribute to increase risk in this regard. We planned this prospective study with the aim to identify such peculiar risk factors in our set-up.

MATERIAL AND METHODS

A descriptive study was conducted in the Department of Pediatric Critical Care Unit (CCU) of the Children's Hospital and the Institute of Child Health, Lahore. A total of 152 children who were diagnosed as DKA admitted in the department of Pediatric CCU between February 2015 to December 2018 were included in the study. Data was collected prospectively by non- probability convenience sampling.

This sample size was calculated by taking the prevalence of DKA as 8% with 95% confidence interval and 5% margin of error by using Openepi sample size calculator. Information about age, new onset or already diagnosed case, febrile illness in recent past, parental education, socioeconomic status, conscious level, time of initiation of treatment, treatment at some other hospital, presence of papilledema, blood sugar (BSR) level and arterial blood gases were taken.

Diagnostic criteria for DKA was hyperglycemia - blood glucose ≥200 mg/dl, pH <7.3 or bicarbonate <15 mmol/l with ketonemia and ketonuria. Delayed treatment was defined as failure to start on specific management of DKA within 3 hours of diagnosis of DKA.

Categorization of severity of DKA was done as: Mild - pH<7.3 or bicarbonate <15 mmol/L, Moderate - pH<7.2 or bicarbonate <10 mmol/L and Severe - pH <7.1 or bicarbonate <5 mmol/L). Cerebral edema was diagnosed if any one of following was present: abnormal motor or verbal response to pain, decorticate or decerebrate posture, abnormal neurogenic respiratory pattern (e.g. Cheyne-Stokes respiration) and papilledema on fundoscopy.

Approval of the study was taken from the the Children's Hospital and the Institute of Child Health, Lahore and informed written consent was taken from parents or caregivers. Data was be analyzed using SPSS-22. The quantitative variables were presented as mean ± standard deviation (SD), while the qualitative variables like clinical symptoms, signs, disease severity and outcome were expressed as frequency and the percentage. Relative risk of developing cerebral edema was estimated and statistical significance was analyzed and chi square was applied for categorical variables and p value <0.05 was considered significant.

RESULTS

A total of 152 patient with DKA were included having mean age of 7.86 ± 4.06 years and

maximum number 64 (42%) were in >10 years of age group. Mean weight of the children was 19.89 ± 8.70 kg. More cases 89 (59%) were of new onset diabetes. Majority belonged to poor social class {134 (88%)} with low parental literacy rates {101 (66%)}. In our study period the case fatality rate of diabetic ketoacidosis was 22 (15%) table 1. Most of the cases were categorized as severe DKA 109 (71%) and 61 (40%) presented with unconsciousness. Clinical Findings and laboratory findings are described in table 2.

TABLE 1: Demographics of Study Participants (n=152)

Characteristics	Number	Percentage
Child's Age (mean ± SD) 7.86 ± 4.06 years		
< 1 year	08	5.3
1 year - <5 years	30	20
5 years - <10 years	50	33
>10 years	64	42
Child Weight (mean ± SD) 19.89 ± 8.70		
Diabetes Onset		
New Onset diabetes	89	59
Diagnosed case of diabetes	63	41
History >1 month duration	51	34
History of fever/infection	90	59
Poor Social Status	134	88
Parental education less than primary	101	66
Delayed Diagnosis	26	17
Diagnosis missed in Emergency Ward	08	05
Initial treatment at periphery	54	36

TABLE 2: Clinical Presentation and Laboratory findings (n=152)

Clinical Presentation and Lab parameters	Number	Percentage
Severity of DKA		
Mild	09	06
Moderate	34	22
Severe	109	71
Unconsciousness at presentation	61	40
Glasgow Coma Scale at admission (mean ± SD) 10.54 ± 3.61		
Papilledema	38	25
Focal Neurological Sign	08	5.3
BSR >500mg/dl at admission	112	74
ABG pH (mean ± SD) 7.039 ± 0.161		
ABG pH <7.0 at admission	73	48
Bicarbonate <5 mmol/L at admission	119	78
Hyponatremia Serum Sodium <130 mEq/L	12	08
Hypernatremia Serum Sodium >145 mEq/L	27	18
Hypokalemia Serum Potassium <3.5 mEq/L	50	33

BSR=Random blood sugar

The factors associated with increased relative risk of cerebral edema were unconsciousness at presentation (OR: 5.470; 95%CI: 2.822-10.603) (p=<0.001), initial treatment at periphery/local hospital (OR: 2.420; 95% CI: 1.449-4.042) (p = 0.001), low bicarbonate level at admission (OR: 11.370; 95% CI: 1.624-79.586) (p=<0.001), pH at admission <7.0(OR:3.968; 95% CI 2.041-7.714) (p = <0.001) , hypernatremia (OR:2.849; 95% CI 1.792-4.529) (p=<0.001) and hypokalemia OR:1.855; 95% CI 1.122-3.064) (p=0.021) table 3).

TABLE-3: Estimated relative risk of various factors with cerebral edema

Factors	Odds Ratio	95% CI	p- Value
New Onset Diabetes	1.416	0.813 - 2.465	0.270
Age	.706	0.359 - 1.389	0.402
Low Socioeconomic Status	2.687	0.709 - 10.180	0.158
Unconsciousness	5.470	2.822 - 10.603	<0.001
Initial treatment at periphery/local hospital	2.420	1.449 - 4.042	0.001
BSR at admission >500mg/dl	1.518	0.769 - 2.997	0.303
Bicarbonate at admission <5mmol/L	11.370	1.624 - 79.586	<0.001
PH at admission <7.0	3.968	2.041 - 7.714	<0.001
Hypernatremia	2.849	1.792 - 4.529	<0.001
Hypokalemia	1.855	1.122 - 3.064	0.021
Delayed diagnosis/treatment	1.720	.999 - 2.960	0.090
Diagnosis missed in emergency ward	.900	0.263 - 3.075	1.000

BSR=Random blood sugar

DISCUSSION

DKA generally tends to occur in persons younger than 19 years, but it may occur at any age in patients with T1DM. In our study the mean age of 7.86 ± 4.06 years is comparable with the study published by Paulina et al. in which the mean age of patients was 7.2 ± 3.4 years.[8] A study published by Hadgu had a higher median age of 11 years as the age of children presenting with DKA ranged between 3 months and 18 years, majority were >10 years of age and only 2% were less than one year of age.[9] We also had comparable results as majority of our patients were >10 years of age. In a research from Poland mean age was 8.9 ± 4.6 year and the age most prone to DKA was below 2 year.[4] Two other researches also showed a slightly higher mean age 8.2 ± 3.5 and 9.1 ± 4.5 years at diagnosis of T1DM.[10,11] The reason of a younger age in our study is probably due to the reason that our hospital is a tertiary care center and we get referral of sick children from different areas of Punjab.

The most common cause was missed diagnosis of diabetes, as 59% of patients presented with DKA in first presentation. DKA was present at diagnosis in about one third of patients in a study by Eyal et al.[11] Missing a diagnosis is common in a research from Korea showing that out of all study population 46.6% were not diagnosed at their first hospital visit and a delay in the diagnosis resulted in increased risk for DKA ($p = 0.002$).[12] Significantly increased risk for DKA was found in children having age ≥12 years, presence of preceding infection, and delay in diagnosis.[12] In our study 59% newly diagnosed cases of TIDM presented with DKA and there was delay in diagnosis of diabetes in our 17% of children. The reason of missing the diagnosis is that the symptoms of T1DM are masked by the symptoms of infection resulting in delayed diagnosis and increased risk for DKA. Similar to our result, research from Ireland had 61% newly diagnosed patients.[13] A much higher percentage (67.4%) and (67.3%) children had not been previously diagnosed with diabetes and were classified in the category of disease diagnosis for the first time as reported by Del Pozo and a study from Poland respectively.[8,14] Comparative to such a high percentage of newly diagnosed cases of diabetes presenting in DKA, a study by Al Shaikh showed the incidence of DKA as 37.7% among newly diagnosed children with T1DM.[15] In two studies by McKenna and Mencher, lowest reported incidence of DKA among newly diagnosed children was 28.7% and 29% respectively.[16,17] Reports from developed world are also not different from the developing countries in which DKA is often diagnosed at first presentation of T1DM and occurs more commonly when a patient is misdiagnosed leading to death in children or having worse long-term outcomes. As compared to those who were correctly diagnosed at presentation the risk of DKA increased by 18% in those children in which the diagnosis was missed at presentation.[18]

In our study the case fatality rate was 15%, mostly in children who had cerebral edema and it is much higher than reported by Aminzadeh et al showing mortality rate of 4% in DKA patients.[14] Research from India stated that patients presenting in shock not responding to fluid therapy and azotemia at the time of admission were more prone to cerebral edema. No association was found between blood glucose level at presentation, effective osmolality or rate of drop in glucose with cerebral edema.[19] Similarly we did not find any association of high blood sugar level with the development of cerebral edema. A study by Bohn narrated that rapid fall of sugar level with insulin therapy and intravenous fluids can result in a rapid reduction in osmolarity and fluid shift thus leading to cerebral edema.[20] In a case–control study, important predictors of risk for cerebral edema were baseline acidosis along with deranged sodium, potassium and urea concentrations.[21] Similarly, a research by Natasha showed that severity of DKA was significantly associated with low pH at admission, low bicarbonate level along with higher initial blood glucose.[22]

Limitations: A single centered study and from a tertiary care hospital where critically sick children are referred limits the generalization of our results. Moreover we did not take into account the rate of drop of sugar level.

CONCLUSION

Unconsciousness at presentation, initial treatment at periphery/local hospital, severe metabolic acidosis, hypernatremia and hypokalemia were

most common risk factors identified for development of cerebral edema among the newly diagnosed T1DM children presenting with DKA. Early identification and promptly addressing the risk factors for development of DKA may decrease the chances of cerebral edema and thus increasing the favorable outcome.

Conflict of interest: Nil

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