ORIGINAL RESEARCH

Initial Laboratory Characteristics and Treatment Related Factors in Relation to Occurrence of Cerebral Edema in Children with Diabetic Ketoacidosis- Experience of a Tertiary Care Center

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ABSTRACT

Background and Objectives: The most gruesome complication of DKA is cerebral edema (CE) as it is not only associated with a high mortality rate but also leads to significant morbidity among the survivors. Therefore, it is prudent that clinicians emphasise on its early recognition so as to intervene quickly and timely. The present study was undertaken to study the association between cerebral edema and demographic features, initial laboratory characteristics and treatment related factors in children presenting with DKA at a tertiary care institute.**Methods:**This hospital-based cohort study was conducted in Paediatrics department of our hospital over three years from October 2019 to September 20222 including children >1 year to <15 years of age presenting to I.P.D or Emergency with DKA. Classification of DKA was done as per ISPAD 2018 guideline and cerebral edema was diagnosed on pre-set clinical criteria. Children with incomplete information regarding their treatment immediately prior to admission at our institute were excluded.**Result:** 118 children with DKA were enrolled over the 3 years out of which 69 were males and 49 were females with male: female ratio of 1.4:1. Mean age was 8.08 ± 3.26 years and mean weight was 19.47 ± 4.34 kg. Overall, 23 (194%) children were diagnosed to be suffering from CE. Children with CE had significantly worse pH, base deficit, bicarbonate level and serum osmolality at admissison. They also had a significantly higher incidence of prior i.v fluid bolus therapy, prior insulin therapy as well as prior bicarbonate therapy than those without CE. Such children also required a significantly longer duration of insulin infusion (37.3 ± 15.2 hours vs 18.4 ± 8.6 hours, $p<0.0001$) as well as a significantly longer duration of ICU stay (4.8±2.5 days vs 2.3 ± 1.1 days, $p<0.0001$).**Conclusion:**Occurrence of CE is related to the severity of underlying initial metabolic disturbances as reflected by a worse pH, base deficit, bicarbonate level and serum osmolality OR to a combination of factors associated with treatment of DKA including prior fluid bolus or insulin or bicarbonate therapy as well as overzealous rehydration of such children.

Key words: cerebral edema, diabetes mellitus, fluid, ketoacidosis, treatment

INTRODUCTION

Diabetic ketoacidosis (DKA) is often the initial presentation of newly diagnosed type 1 or type 2 diabetes mellitus in young children as well as adolescents. It is estimated that about one-third of children with newly diagnosed diabetes mellitus land up in paediatric emergency unit with DKA.[1] However, it may also present later in the course of disease process as a result of infection or other stress factors or non-compliance with treatment. The most gruesome complication of DKA is cerebral edema (CE) as it is not only associated with a high mortality rate[2] but also leads to significant morbidity among the survivors.[3] Infact, some studies have revealed that cerebral edema is still the cause of mortality in more than half of total diabetes-related deaths in paediatric age group.[4,5]

CE occurs rarely in adults and children in their late teenage. Such age-related pathogenesis may be probably due to difference in brain metabolism in children where the latter's brains have greater substrate and oxygen requirements as well as greater sensitivity to hypoxic damage as compared to their adult counterparts. Even in paediatric age group, the time of onset of cerebral edema is quite variable among the subjects.[6] Nearly two-thirds of such children start exhibiting clinical features of CE within the first 8 hours of hospitalisation and the rest show them after 12-24 hours of hospitalisation with passage of some time after treatment has begun. Such children with early-onset CE have been found to be of a relatively younger age, but the therapeutic implication of this finding is inconclusively known. The exact mechanism and pathogenesis of cerebral edema in DKA still remains much elusive. Development of cerebral edema sets in before treatment has begun, so it is not entirely iatrogenic. Additional neuronal injury does occur during treatment of DKA, so iatrogenic component cannot be entirely ruled out as well. For example, overzealous rehydration with hypotonic fluid and/or exogenous bicarbonate or phosphate administration has been shown to induce or worsen cerebral edema once it has set in.[7] The absence of a clear understanding of the pathogenesis of this dreaded condition and its prevention mandates that clinicians must emphasise on its early recognition so as to intervene quickly and timely in order to reduce its morbidity and mortality. Clinical studies, most of them small, have not shed much light on the factors predicting its occurrence.[8,9] Based on this background, we conducted this study at our tertiary care centre to study the time course and factors associated with CE in children being treated for DKA.

Aim and Objectives

To study the association between cerebral edema and demographic features, initial laboratory characteristics and treatment related factors in children presenting with DKA at our institute.

MATERIALS AND METHODS

Study duration: three years fromOctober 2019 to September 2022

Study setting: I.P.D and E.R of deptt of Paediatrics of Nalanda Medical College and Hospital. Patna, Bihar, India.

Study design: hospital-based cohort study.

Inclusion criteria: Children >1 year to <15 years of age presenting to I.P.D or E.R of our deptt with features suggestive of DKA were screened for eligibility in the present study.Diagnosis and classification of DKA was done as per 2018 guidelines of International Society for Paediatric and Adolescent Diabetes (ISPAD).[10] Cerebral edema was diagnosed on the basis of following: any child with DKA without a previous history of neurological disease having abnormal neurological findings such as altered sensorium, abnormal posturing, seizures, cranial nerve palsy or respiratory failure that showed a prompt response to mannitol osmotherapy with or without radiological features of cerebral edema on a cranial CT imaging, was labelled as a child having cerebral edema.

Exclusion criteria: Children receiving systemic steroids for >2 weeks and children with other endocrinal disorders causing diabetes like picture e.g., Cushing's syndrome, acromegaly were not enrolled. Children with incomplete information regarding their treatment immediately prior to admission at our institute were excluded to remove treatment related unknown confounding factors.

Data collection: After obtaining written informed consents from the parents, potential children were enrolled in this study. Detailed history and focussed clinical examination were done for all such patients. A structured proforma was used to obtain information about demographic factors (such as age, sex, weight, duration and the type of diabetes, previously diagnosed or new onset diabetes etc), precipitating events if known (such as a recent illness, infection, missed insulin dose, fasting etc) and immediate previous treatments received elsewhere (bolus dose of insulin, type and volume of fluid therapy and bicarbonate or phosphate infusion). Management of children was done as per ISPAD guidelines. Information related to post hospitalisation events were also collected and recorded in the proforma (duration and dose of insulin infusion, time of onset of cerebral edema and its management, course and duration of hospital stay and outcome).

Statistical Analysis: Information so collected was tabulated and entered in Microsoft excel sheet and further analysed by SPSS ver.20® software for Windows. Variables were expressed as mean, standard deviation, percentages, proportions or percentiles as appropriate. We used Pearson's chi-square test for categorical parameters and independent samples' t test for continuous parameters. P-value <0.05 was taken as significant.

RESULTS

Over the 3 year study period we enrolled 118 patients with DKA in this study out of which 69 were males and 49 were females with male: female ratio of 1.4:1. This sex difference was not statistically significant (p=0.07). Mean age of the study participants was 8.08 ± 3.26 years and mean weight of the children was 19.47 ± 4.34 kg. Among them, 53 (44.9%) were unaware that they had been having this disease. At the time of admission, 11 (9.3%) children had mild DKA, 43 (36.5%) had moderate DKA and 64 (54.2%) had severe DKA. Mean arterial pH on admission was 7.06 ± 0.14. Overall, clinically apparent CE was noticed in 23 (19.5%) children during their period of hospitalisation. Of these, 19(16.1%) had evidence of CE by the time they were brought to our institute from elsewhere while 4 (3.4%) developed it later during hospital stay: 3 of these children developed CE within the first 24 hours of hospitalisation while the rest 1 developed it after 48 hours as a result of refractory metabolic acidosis. Mean duration post hospitalisation when cerebral edema was diagnosed in these 4 children was 16.3 ± 8.7 hours. Demographic and initial laboratory parameters of children with and without CE at admission is shown in table below. The two groups didn't differ significantly in terms of age, sex, blood glucose, urea, creatinine, sodium, potassium, chloride, pO2, or pCO2. However, the group with CE had significantly worse pH, base deficit, bicarbonate level and serum osmolality. Interestingly, children with CE also had a significantly higher proportion of children with newly diagnosed diabetes mellitus, higher proportion of severe DKA, pH <7 and pCO2 <10 mmHg.

Table1: Demographic, clinical and initial laboratory parameters in children with and without CE

Parameters	**Cases without CE (n= 95)**	**Cases with CE (n=23)**	**p value**
Age in years (Mean ± SD)	8.4 ± 3.5	7.1± 2.4	0.09
Male gender (number, percentage)	55, 57.9%	14, 60.9%	0.79
Newly diagnosed diabetes (number, Percentage)	38, 40.0%	15, 65.2%	**0.03**
Features of shock at admission (number, percentage)	12, 12.6%	6, 26.1%	0.10
Severe DKA (number, percentage)	47, 49.5%	17, 73.9%	**0.03**
Blood glucose at admission in mg/dl (Mean ± SD)	492.3 ± 89.5	530.2±95.7	0.07
Arterial pH (Mean ± SD)	7.12±0.19	6.96±0.11	**0.001**
Arterial pH less than 7.0 at admission (number, percentage)	28, 29.5%	12, 52.2%	**0.04**
Serum Bicarbonate (Mean ± SD)	7.1±3.4	4.9±2.1	**0.004**
Base deficit (Mean ± SD)	18.3±4.4	20.8±4.9	**0.01**
pO_2 in mmHg (Mean ± SD))	92.4±12.3	89.4±11.8	0.29
pCO_2 in mmHg (Mean ± SD)	21.6±5.3	19.3± 4.9	0.06
pCO_2 <10 on admission (number, percentage)	17, 17.9%	11, 47.8%	**0.003**
Serum osmolality in mOsm/L (Mean ± SD)	321.4±15.1	329.2±16.3	**0.03**
Serum Sodium in mEq/L (Mean ± SD)	134.3± 4.8	132.9±4.2	0.17
Serum potassium in mEq/L (Mean ± SD)	4.6±0.8	4.3±0.7	0.10
Serum chloride in mEq/L (Mean ± SD)	105.3±9.4	109.1±9.9	0.09
Blood urea in mg/dl (Mean ± SD)	48.3±8.1	52.1±9.7	0.06
Serum Creatinine in mg/dl (Mean ± SD)	0.92±0.14	0.98±0.16	0.07

(CE= cerebral edema, S.D = standard deviation)

Treatment related factors before as well as after admission to our institute that could have contributed to the development of cerebral edema were studied in all children as depicted in table 2 below. Prior fluid therapy, time of starting hypotonic fluids and timing or dose of insulin therapy was not significantly different between the 2 groups. Children with CE had a significantly higher incidence of prior i.v fluid bolus therapy, prior insulin therapy as well as prior bicarbonate therapy than those without CE. Children with CE also had a significantly higher incidence of reduction of serum osmolality >20 mOsm/kg during the first 6 hours of treatment.

Table 2: Comparison of treatment related factors in the two groups

Parameters	**Cases without CE (n= 95)**	**Cases with CE (n=23)**	**p value**
Prior i.v fluid therapy (number, percentage)	64, 67.4%	20, 86.9%	0.06
Prior bicarbonate therapy (number, percentage)	12, 12.6%	8, 34.8%	**0.01**
Prior s.c insulin therapy (number, percentage)	23, 24.2	11, 47.8%	**0.02**
Prior i.v fluid bolus therapy (number, percentage)	15, 15.8%	9, 39.1%	**0.01**
Time of initiation of i.v insulin therapy after admission in minutes, (Mean ±SD)	24.3±8.7	29.1±9.4	0.07
Dose of i.v insulin therapy during the first 4 hour in U/kg	0.096±0.007	0.098±0.008	0.23

(Mean±SD)			
Volume of fluid infused over first 4 hours of therapy in ml/kg/4 hour (Mean±SD)	23.5±3.8	25.8±4.4	**0.01**
Time of starting hypotonic fluid infusion in hours (Mean± SD)	2.6±1.2	2.8±1.3	0.48
Fall of >20 mOsm/kg in serum osmolality during the first 6 hour of treatment (number, percentage)	8, 8.4%	6, 26.1%	**0.02**

Outcome: With standard treatment as per protocol, hyperglycaemia, ketonemia and acidosis started gradually improving and their respective mean duration of resolution was 11.6 ± 5.3 hours, 17.9 ± 6.7 hours and 25.8 ± 12.1 hours. Ventilatory support was required in 9 (39.1%) children with CE and 1 (4.3%) child required dialysis for acute renal injury. None of the child without CE features required ventilatory support or dialysis. Children with CE required a significantly longer duration of insulin infusion (37.3 ± 15.2 hours vs 18.4 ± 8.6 hours, $p<0.0001$) as well as a significantly longer duration of ICU stay (4.8±2.5 days vs 2.3 ± 1.1 days, $p<0.0001$). Of these 23 children with CE, 14 (60.9%) had full recovery without neurological sequelae, 4 (17.4%) recovered but were left with neurological sequelae and 5 (21.7%) couldn't survive. Primary cause of mortality in these 5 children were ARDS in 2, cerebral herniation syndrome with its complications in 2 and AKI in 1.

DISCUSSION

The present study was conducted at our tertiary care level institute to study the association between cerebral edema and demographic features, initial laboratory characteristics and treatment related factors in children presenting with DKA. Incidence of cerebral edema in DKA in this study was 19.5% which is lower than the findings of Tiwari et al[11] but considerably higher than incidence of 0.5-1.5% reported in population-based studies.[12] This can be attributed to the referral bias resulting in admission of more sick patients at our institute. However, 82.6% of all children who ultimately suffered from CE could be diagnosed at the time of admission in our study which is considerably higher than the corresponding figure of 22.2% children as reported by Jayashree et al.[13] This can be explained by higher proportion of children with severe DKA &/or delayed diagnosis and inappropriate treatment before admission to our institute.

Similar to the finding of large case control study of Edge et al,[14] we did not find a significant age difference between children with and without CE. The present study also supports the notion that severe acidosis is one of the major risk factors for development of CE in DKA as it diminishes cerebral blood flow and inhibits the activity of pH-dependent glycolytic enzymes.[15] Correspondingly, in our study children with CE had significantly worse pH, base deficit and bicarbonate level. It has also been hypothesized that CE might be precipitated or aggravated by some treatment related factors. In this study we found that a significantly higher proportion of children with CE had received i.v fluid bolus or s.c insulin or bicarbonate therapy prior to admission in our hospital. Moreover, after admission a significantly higher proportion of children with CE had received greater volume of fluid infused initially and they had experienced fall of >20 mOsm/kg in serum osmolality during the first 6 hour of treatment. These findings support the hypothesis that bicarbonate treatment might aggravate CE due to cerebral hypoxia or paradoxical acidosis of the cerebrospinal fluid.[16] Significantly higher volume of fluid administration during the initial hours of treatment in CE group supports the concept that CE develops due to rapid reperfusion injury following initial cerebral hypoperfusion. The present study has demonstrated favourable outcome in nearly 4 out of every 5 child admitted with CE despite the need for ventilatory support in nearly 40% of all such children. Moreover, the primary cause of mortality in this study was related to cerebral edema in less than 50% cases and the rest had non- CE related causes (renal failure in one and ARDS in other 2). This could be achieved by anticipation, close clinical observation, timely identification and prompt treatment. Not only mortality, presence of CE also imposes significant morbidity in these children. This was evident by almost doubling of duration of insulin infusion and ICU stay of such children in our study which is comparable to reports of cerebral edema associated increased hospital stay[17] and yet again emphasises the need for early diagnosis and timely referral of DKA. For a resource limited country like ours, this study strongly suggests that all clinicians dealing with children with DKA should specify the type and amount of i.v fluid therapy before referral so that un-necessary fluid administration and subsequent development/worsening of CE can be avoided.

CONCLUSION

Occurrence of CE in children with DKA is related to the severity of underlying initial metabolic disturbances as reflected by a worse pH, base deficit, bicarbonate level and serum osmolality OR to a combination of factors associated with treatment of DKA including prior fluid bolus or insulin or bicarbonate therapy as well as overzealous rehydration of such children. Until the exact pathophysiology of CE in DKA is fully understood, primary prevention of DKA in children with type 1 diabetes would remain the only reliable means to avoid this potentially life-threatening complication.

Limitations

The present study has few limitations. First, it is a single centre tertiary care hospital based study and so the majority of patients we treated were generally very sick. Second limitation is related to relatively smaller number of children with CE due to which a multivariate analysis was not performed. Third, long term follow-up of children with CE was not done. Fourth, cerebral edema was diagnosed on the basis of clinical features and not confirmed radiologically. However, this is the usual practice globally and represents the standard of clinical care. Moreover, delay in treatment for radiological confirmation can be counterproductive at times.

Conflict of interest: None to declare.

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