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Risk Factors for Cerebral Oedema in Children With Diabetic Ketoacidosis

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Abstract:

Background: The risk factors for this uncommon life-threatening complication haven't been defined clearly yet.

Method: We analyzed the biochemical and therapeutic risk factors for cerebral oedema in diabetic ketoacidosis by a retrospective study of 171 children admitted to two hospitals for diabetic ketoacidosis between January 2022 and January 2023. A comparison was made between the cases with and without cerebral oedema in demographic and biochemical variables at presentation and therapeutic interventions. cerebral oedema was diagnosed in 15 (8.8%) of 171 cases included in the study. The outcome was fatal only in one of these cases (7%).

Results: cerebral oedema had a significant association with the severe type of diabetic ketoacidosis at presentation i.e. low venous pH ($p < 0.001$), low sodium bicarbonate level ($p < 0.001$), and low partial pressure of arterial carbon dioxide PCO2 ($p < 0.001$), high blood glucose ($p < 0.01$), high blood urea ($p < 0.05$) and high serum osmolality ($p < 0.05$). During the treatment of diabetic ketoacidosis, cerebral oedema had a significant association with a low level of serum phosphate ($p < 0.05$). Development of cerebral oedema was also significantly associated with the initiation of management for diabetic ketoacidosis before hospitalization in our hospital ($p < 0.05$), treatment with sodium bicarbonate ($p < 0.001$), higher volume of fluid given initially ($p < 0.01$) and delay in potassium substitution ($p < 0.01$).

Conclusions: Severe cases of ketoacidosis, hyperglycemia and dehydration at presentation, and low serum phosphate during treatment are significantly related to cerebral oedema formation in children with diabetic ketoacidosis. The initial severe acidosis and hyperglycemia probably lead to brain injury, which in turn causes cerebral oedema in the course of developing hypophosphatemia and cerebral hypervolemia.

Introduction:

Diabetic ketoacidosis occurs in 20-40% of children with new-onset diabetes and in children with known diabetes who omit insulin doses or who don't successfully manage an intercurrent illness [1]. It is the primary cause of death for children with diabetes, especially if complicated by cerebral oedema, the causes and the pathogenesis that result in this life-threatening complication haven't been defined clearly yet and there is little information known about the mechanisms of CNS injury [2].

Cerebral oedema is one of the most devastating complications of diabetic ketoacidosis, it is the leading cause of diabetic ketoacidosis mortality in 90% of cases [3]. The incidence of cerebral oedema in children with diabetic ketoacidosis hasn't changed over the past 15-20 yr, despite the widespread introduction of gradual rehydration protocols during this interval [1]. Severe cerebral oedema can lead to brain herniation, which causes permanent neurological damage or even death; however, the data about the incidence and outcomes of cerebral oedema in patients with diabetic ketoacidosis are still limited [4].

Recent studies suggest that cerebral hypoperfusion with subsequent reperfusion of previously ischaemic brain tissue may be related to vasogenic oedema during diabetic ketoacidosis treatment [5]. Furthermore, many studies prove that diabetic ketoacidosis causes inflammatory changes in the brain, including reactive gliosis and activation of microglia, during untreated diabetic ketoacidosis but intensifying during treatment with insulin and saline [6].

Our study aims to identify the initial biochemical and therapeutic risk factors for cerebral oedema in children with diabetic ketoacidosis.

Subjects and methods:

We examined the medical records of 171 cases with diabetic ketoacidosis aged 0–15 years who were admitted between January 2022 and January 2023 in Maternity and Children Teaching Hospital and Al-Hussein Pediatric Hospital in Al Diwaniyah Governorate, Iraq.

The following data from the record of each patient were recorded: demographic characteristics, initial biochemical values, treatment regimen, and changes in laboratory values during treatment., complications, and outcome.

Calculation of total serum osmolality (mOsm/kg) was made by the formula [7] :

$2 \times [Na^+]$ corrected (mmol/L) + [serum K^+] (mmol/L) + [serum urea] (mmol/L)+ [serum glucose] (mmol/L), where:

$[Na^+]$ corrected = $[Na^+]$ measured + $2 \times \{([\text{plasma glucose}] - 5.6)/5.6\}$

All 171 cases met the diagnostic biochemical criteria for diabetic ketoacidosis which are:

1) Hyperglycemia (blood glucose more than 11 mmol/L).
2) Venous pH less than 7.3 or bicarbonate less than 15 mmol/L.
3) Ketonuria.

The *Diagnostic* criteria of cerebral oedema are:

1) Abnormality in motor or verbal responses to pain.
2) Decorticate or decerebrate posture.
3) Abnormal neurogenic respiratory pattern (e.g. Cheyne–Stokes respiration).
4) Cranial nerve palsy.

The *Major* criteria are:

1) Altered level of consciousness.
2) Sustained heart rate deceleration (decrease of more than 20 beats/min) not attributable to improved intravascular volume or sleep state.
3) Age-inappropriate incontinence.

The *Minor* criteria are:

1) Vomiting.
2) Age less than 5 yr.
3) Headache.
4) Lethargy or not easily arousable.
5) diastolic blood pressure of more than 90 mmHg.

One diagnostic or two major criteria, or a combination of one major and two minor criteria, were used to identify cerebral oedema [8].

Patients who need treatment with mannitol, intubation, computed tomographic scanning, or magnetic resonance imaging are also considered to have cerebral oedema.

All 15 cases that met these criteria had specific treatment for cerebral oedema. Clinical improvement occurred in 14 of them and only one case had a fatal outcome.

Statistical analysis:

Data were processed by using version 22.0 (SPSS) comparison between groups. The differences were statistically significant at $p < 0.05$.

Results:

Cerebral oedema was observed in 15 (8.8%) of all 171 cases hospitalized for diabetic ketoacidosis during the study period. The neurologic deterioration occurred in the 1st 24 hours after hospitalization. Of all the 15 children with cerebral oedema, one (7%) died.

Initial variables (the 1st records before treatment was started):

Regarding patients with cerebral oedema at presentation (Table 1):

1) No age-dependent difference between the patients with and without cerebral oedema ($p > 0.05$).
2) Highly significant more severe acidosis: low venous pH, serum bicarbonate, and partial pressure of arterial carbon dioxide PCO2 ($p < 0.001$).
3) Significantly high serum glucose ($p < 0.01$).
4) Significantly high urea nitrogen ($p < 0.05$).
5) Significantly high serum osmolality ($p < 0.05$).
6) No statistically significant differences were proved in potassium levels ($p > 0.05$).

Therapeutic variables:

Analyzation of the relationship between development of cerebral oedema and therapeutic activities proves the following:

1) A significant number of cases with cerebral oedema had received some treatment for diabetic ketoacidosis before they were referred to our hospital ($p < 0.05$).
2) Treatment with sodium bicarbonate and a smaller increase in serum sodium concentration during therapy had a significant association with cerebral oedema ($p < 0.001$).
3) There is no evidence that either the dose of intravenous insulin or the earlier initiation of insulin treatment was statistically significant in association with cerebral oedema ($p > 0.05$).
4) No significant association between the time of addition of glucose solution (ratio of 1:1 or greater with 0.9% NaCl) and the development of cerebral oedema, i.e. cerebral oedema wasn't related to earlier infusion of hypotonic solutions.
5) The cumulative volume of intravenous fluid given over the 1st 4 hr (mL/kg) had a significant association with cerebral oedema ($p < 0.01$). Patients with this complication had received about 35 mL/kg intravenously in the 1st 4 h, while patients without cerebral oedema had received about 24 mL/kg in the same period.
6) After the fourth hour, the time before initiation of potassium infusion, had a significant relation to the development of cerebral oedema ($p < 0.01$).

7) Both groups, with and without cerebral oedema, became hypophosphatemic 6–12 hr after therapy started, but the patients with cerebral oedema had significantly low levels of phosphate during the treatment ($p < 0.05$).

8) No significant association between the drop in serum osmolality by more than 20 mOsm/kg during the 1st 6 hr of treatment and the development of cerebral oedema.

Table (1) Comparative analysis of Demographic, laboratory data, and some treatment factors of diabetic ketoacidosis cases with and without cerebral oedema.

	Variable	Patients without cerebral oedema n=156			Patients with cerebral oedema n=15			p-value	Statistical significance
		n	Mean	SD	n	Mean	SD		
Initial data	Age (years)	156	11.32	4.80	15	8.90	4.20	> 0.05	No significance
	Venous pH	156	7.12	0.10	15	6.94	0.10	< 0.001	Highly significant
	Bicar. (mmol/L)	156	5.34	2.60	15	3.30	1.29	< 0.001	Highly significant
	PCO2 (mmHg)	156	16.55	5.30	15	14.72	5.70	< 0.001	Highly significant
	Bl.glucose (mmol/L)	156	22.40	5.75	15	26.33	5.75	< 0.01	Significant
	S.urea (mmol/L)	90	5.21	2.42	9	6.51	2.49	< 0.05	Significant
	S.osmolality (mOsm/kg)	156	321.48	16.21	13	331.6	15.44	< 0.05	Significant
	S.sodium (mmol/L)	101	138.70	6.32	9	139.57	7.69	> 0.05	No significance
	S.potassium (mmol/L)	101	4.67	1.05	9	4.20	0.85	> 0.05	No significance
	S.phosphate (mmol/L)	66	1.47	0.63	7	1.50	0.70	> 0.05	No significance
During treatment	Patients had received treatment for DKA before referral to	6			2			< 0.05	Significant

	our hospital								
	Time of initiation of intravenous insulin (min)	153	27.6	52.11	13	35.4	55.4	> 0.05	No significance
	Dose of intravenous insulin in the 1st 4 hr (IU/kg/hr)	137	0.10	0.00	15	0.10	0.00	> 0.05	No significance
	Fluid volume infused in 1st 4 hr (mL/kg/4 h)	153	24.01	10.00	13	34.88	15.04	< 0.01	Significant
	Starting time of infusion of hypotonic solutions (hr)	104	2.22	1.40	7	2.61	1.67	> 0.05	No significance
	Time of initiation of potassium (h)	154	2.55	1.50	15	4.30	2.60	< 0.01	Significant
	Treated with bicarbonate	25			9			< 0.001	Highly significant
	S.phosphate at 6th-12th hr during treatment (mmol/L)	44	0.88	0.40	7	0.55	0.39	< 0.05	Significance

Discussion:

Symptomatic cerebral oedema occurred in approximately 1 percent of the episodes of diabetic ketoacidosis. Asymptomatic cerebral swelling is thought to occur more frequently [9].

The incidence of cerebral oedema in diabetic ketoacidosis in our study (8.8%) was more than that reported in many national population studies, 0.5%–1.5% [10,11,12], but much less than that reported by Tiwari et al (26%) [13].

As with several previous investigations, [14] the current study proves that cerebral oedema can develop in some cases of diabetic ketoacidosis before the initiation of treatment, but the variations in treatment can increase the ongoing pathologic process.

In our study, similar results from large case-control studies in the U.S.A, U.K, and Canada, younger age wasn't found to be related to the development of cerebral oedema. [10,11,15]

We support the suggestion that severe acidosis is one of the major risk factors for cerebral oedema in diabetic ketoacidosis (The incidence of cerebral oedema was significantly higher in children with venous pH ≤ 7.1), it diminishes cerebral blood flow and inhibits the activity of pH-dependent glycolytic enzymes [16]. Recently, it has been shown that the severity of acidosis correlates with alterations in the expression of matrix metalloproteinases, which in turn mediate blood–brain barrier dysfunction during diabetic ketoacidosis [17].

Some aspects of treatment did appear to be related to the development of cerebral oedema, particularly the bicarbonate treatment and the delayed potassium substitution. These results agree with many previous reports that implicated the use of bicarbonate as a risk factor for cerebral oedema due to cerebral hypoxia [10,11,18].

In our study, in accordance with the study of Edge et al., [15] the larger fluid volumes infused during the 1st 4 hr were associated with development of cerebral oedema. These results support the hypothesis that cerebral hypoperfusion before treatment for diabetic ketoacidosis, followed by rapid reperfusion, may be an important cause of cerebral injury and cerebral oedema [19].

Our study showed a significant association between low serum phosphate levels during treatment and the development of cerebral oedema. In diabetes, the lowest concentration of phosphate is associated with the highest consumption of oxygen [20]. When phosphate and/or oxygen are insufficient for high-energy phosphate synthesis, cell homeostasis can't be maintained and cell integrity may be impaired, including the integrity of blood–brain barrier [21].

A decrease in phosphate level leads to a decrease in ATP level and erythrocyte 2,3-bisphosphoglycerate concentration, this will shift the oxygen dissociation curve to the left and decrease oxygen delivery to the tissues. Hypoxia or intracellular acidosis induces elevation in the erythrocyte 2,3-bisphosphoglycerate and capillary vasodilation. When the elevation of red-cell 2,3-bisphosphoglycerate isn't appropriate (which occurs in the case of hypophosphatemia), the tissue oxygen demand is no longer met by the oxygen delivery. This results in massive capillary vasodilation with increased vascular permeability and plasma leakage into the interstitium which results in oedema, affecting the brain and lungs [22].

Our study supports the hypothesis that cerebral oedema in cases with diabetic ketoacidosis is related to brain ischemia. Both hypocapnia, which causes cerebral vasoconstriction, and severe dehydration will lead to decreased perfusion of the brain [23]. Hyperglycemia superimposed on an ischemic insult aggravate the blood–brain barrier dysfunction, the extent of neurologic damage, and oedema formation [24]. This interaction explains the association of neurologic damage with minor degrees of cerebral hypoperfusion.

Blood–brain barrier dysfunction and vasogenic oedema may occur several hours after an ischemic insult as a result of the release of vasoactive substances and mediators of inflammation [25]. So, cerebral oedema which occurs several hours after the initiation of treatment correlates with the hypothesis that the basis of this complication is ischemia.

Finally, cerebral oedema in children occurs more frequently than in adults, this can be explained by the fact that children's brains have higher oxygen requirements than adults' brains and are thus more susceptible to ischemia [26].

Conclusion:

In this study of children with diabetic ketoacidosis, we evaluated the associations between cerebral oedema and the following factors:

demographic characteristics and initial biochemical characteristics, therapeutic interventions, and changes in biochemical values during treatment.

The development of cerebral oedema in cases with diabetic ketoacidosis may be related to the severity of underlying metabolic disturbances or a combination of factors associated with diabetic ketoacidosis treatment, including decrease level of serum phosphate during therapy. The primary prevention of diabetic ketoacidosis will remain the only reliable means to avoid cerebral oedema in children with type 1 diabetes until the causes of this life-threatening complication become fully understood.

Children with these biochemical features which are mentioned in Table (1), should be monitored closely for signs of neurologic deterioration, and hyperosmolar therapy should be available for immediate use if early signs of cerebral oedema occur.

Finally, treatment with bicarbonate should be avoided in most circumstances because it is associated with an increased risk of cerebral oedema.

Conflict of interest:

No potential conflict of interest was reported by the authors.

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