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RISK FACTORS FOR CEREBRAL EDEMA IN CHILDREN WITH DIABETIC KETOACIDOSIS

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ABSTRACT **BACKGROUND:** Cerebral edema is an uncommon but devastating complication of diabetic ketoacidosis in children. Risk factors for this complication have not been clearly defined. **METHODS:** In this multicenter study, we identified 20 children who had been hospitalized for diabetic ketoacidosis within a 2year period June 2018 to June 2020 and in whom cerebral edema had developed. One additional group of 60 childrens with diabetic ketoacidosis but without cerebral edema was also identified. Using logistic regression, we compared the two groups with respect to demographic characteristics and biochemical variables at presentation and compared the matched groups with respect to therapeutic interventions and changes in biochemical values during treatment. **RESULTS:** A comparison of the children in the cerebral- edema group with those in the random control group showed that cerebral edema was significantly associated with lower initial partial pressures of arterial carbon dioxide (relative risk of cerebral edema for each decrease of 7.8 mm Hg [representing 1 SD], 3.4; 95 percent confidence interval, 1.9 to 6.3; P<0.001) and higher initial serum urea nitrogen concentrations (relative risk of cerebral edema for each increase of 9 mg per deciliter [3.2 mmol per liter] [representing 1 SD], 1.7; 95 percent confidence interval, 1.2 to 2.5; P=0.003). Of the therapeutic variables, only treatment with bicarbonate was associated with cerebral edema, after adjustment for other covariates (relative risk, 4.2; 95 percent confidence interval, 1.5 to 12.1; P=0.008). **CONCLUSIONS:** Children with diabetic ketoacidosis who have low partial pressures of arterial carbon dioxide and high serum urea nitrogen concentrations at presentation and who are treated with bicarbonate are at increased risk for cerebral edema.

KEYWORDS :

INTRODUCTION

Diabetic ketoacidosis occurs in 25 to 40 percent of children with newly diagnosed type 1 diabetes mellitus[1,2] and may later recur in association with illness or noncompliance with treatment. Clinically apparent cerebral edema occurs in approximately 1 percent of episodes of diabetic ketoacidosis in children and is associated with a mortality rate of 40 to 90 percent[3-6] Cerebral edema is responsible for 50 to 60 percent of diabetes- related deaths in children[7,8] The pathophysiologic mechanism underlying the cerebral edema associated with diabetic ketoacidosis is controversial. Clinical studies to date, most of which have been small, have provided little information about predictive factors. In this case–control study of children with diabetic ketoacidosis, we evaluated the associations between cerebral edema and the following factors: demographic characteristics and initial biochemical characteristics, therapeutic interventions, and changes in biochemical values during treatment.

METHODS

Study Subjects

Cerebral-Edema Group

We identified all the children (persons «18 years of age) in whom cerebral edema related to diabetic ketoacidosis admitted between June2018 and June2020 at Dept of Paediatrics,JLNMCH Bhagalpur. To be included in the study, children identified as having cerebral edema were required to meet all the following criteria: the presence of diabetic ketoacidosis (defined as a serum glucose concentration >300 mg per deciliter [16.7 mmol per liter], a venous pH <7.25 or a serum bicarbonate concentration <15 mmol per liter, and the presence of ketones [acetoacetate] in the urine); alteration in mental status (obtundation or disorientation); and either radiographically or pathologically confirmed cerebral edema or specific treatment for cerebral edema (hyperosmolar therapy or controlled hyperventilation) that was followed by clinical improvement. Because cerebral infarction may occur as a consequence of cerebral edema or impending herniation,[9,10] radiographic studies of children with cerebral infarction were also reviewed by a neuropathologist.

Control Groups

For each child with cerebral edema, we identified three other children who were designated as controls. Control group consisted of children with diabetic ketoacidosis (as defined above) who were randomly selected with use of a computer-generated list of numbers from among all the children admitted for diabetic ketoacidosis at JLNMCH during the study period.

Data Collection

The following data from each child were recorded: demographic characteristics, initial biochemical values, treatment regimen, and changes in laboratory values during treatment. We calculated other variables according to the following formulas[11-14] : corrected serum sodium concentration=measured serum sodium concentration+([(serum glucose concentration-100)÷100] 1.6), with the serum glucose concentration expressed in milligrams per deciliter; osmolality=(2¬serum sodium concentration)+(serum glucose concentration÷18)+(serum urea nitrogen concentration÷2.8), with the serum sodium concentration expressed in millimoles per liter and the serum glucose and serum urea nitrogen concentrations in milligrams per deciliter; arterial pH=venous pH+0.05; and the partial pressure of arterial carbon dioxide=the partial pressure of venous carbon dioxide-6. Information from nursing records about treatments given during each hour was used to calculate the rates of administration of fluid, sodium, and insulin.

Statistical Analysis

We compared the cerebral-edema group with the random control group by means of a logistic-regression analysis that included the demographic variables and initial biochemical variables, as well as the therapeutic variables and changes in biochemical variables during therapy. Because the odds ratio approximates the relative risk of diseases with a low incidence, we computed the odds ratio to estimate the relative risk. If two or more variables were collinear, only the variable that was measured most frequently was included in the multivariate analysis.

RESULTS

The diagnosis of cerebral edema was based on deterioration in mental status accompanied by radiographic evidence in 10 of the 20 children (50 percent), by changes in mental status that improved after therapy for suspected cerebral edema in 09 children (45 percent), and by postmortem findings in 1 child (5 percent). Neurologic deterioration occurred a median of 7 hours (range, 0 to 25) after the initiation of therapy for diabetic ketoacidosis, but in two of the children (10 percent), all of whom had radiographically apparent cerebral edema, it occurred before the initiation of therapy.

Of the 20 children with cerebral edema, 11 (55 percent) recovered without sequelae, 04 (20 percent) survived with permanent neurologic

dysfunction, and 04 (20 percent) died. During the study period,one other child died as a result of diabetic ketoacidosis, owing to cardiac arrest associated with hypokalemia and hypocalcemia.

Demographic and Initial Biochemical Variables

The 20 children in whom cerebral edema occurred were younger, and more likely to have newly diagnosed diabetes than the 60 children in the control group (Table 1). The children with cerebral edema also had more severe acidosis and hypocapnia and higher serum glucose, urea nitrogen, and creatinine concentrations at the time of presentation than the selected controls.

Table 1. Characteristics Of The Children At The Time Of Presentation.*

Variable	Children With Cerebral Edema (N=20)	Controls (n=60)
Age (yr)	8.9±4.2	11.3±5.0
Male sex (%)	57	41
Newly diagnosed diabetes (%)	66	39
Serum bicarbonate (mmol/liter)	5.9±2.7	7.9±3.6
Serum urea nitrogen (mg/dl)	27±14	20±9
Serum creatinine (mg/dl)	1.5±1.1	1.1±0.7
Serum glucose (mg/dl)	400±150	350±100
Arterial pH	7.06±0.10	7.12±0.11
Partial pressure of arterial carbon dioxide (mm Hg)	11.3±6.5	17.9±7.8

*Plus–minus values are means ±SD. To convert the values for serum urea nitrogen to millimoles per liter, multiply by 0.36; to convert the values for serum creatinine to micromoles per liter, multiply by 88.4; and to convert the values for serum glucose to millimoles per liter, multiply by 0.056.

Comparison of the Children with Cerebral Edema and the Random Controls

In the multiple logistic-regression analysis, the only variables that were associated with cerebral edema, after adjustment for other covariates, were the serum urea nitrogen concentration and partial pressure of arterial carbon dioxide at the time of presentation (Table 2).

Because both arterial pH values and serum bicarbonate concentrations are measures of the degree of acidosis and thus are collinear, we included only the latter in the main multivariate analysis. Likewise, when serum osmolality was substituted for the serum sodium, glucose, and urea nitrogen concentration in a subanalysis, it was not a significant predictor of the risk of cerebral edema. However, the initial partial pressure of arterial carbon dioxide continued to be a significant predictor of the risk of cerebral edema .

Table 2. Multivariate Analysis Of Risk Factors For Cerebral Edema In The Children With Cerebral Edema As Compared With The Random Control Group.*

VARIABLE†	Relative Risk (95% CI)	P Value
Male sex	0.9 (0.4–1.8)	0.68
New onset of diabetes	1.3 (0.5–3.1)	0.57
Age (per 1-yr increase)	0.9 (0.9–1.0)	0.20
Initial serum sodium concentration (per increase of 5.8 mmol/liter)	0.8 (0.6–1.1)	0.19
Initial serum glucose concentration (per increase of 244 mg/dl)	1.0 (0.7–1.5)	0.98
Initial serum urea nitrogen concentration(per increase of 9 mg/dl)	1.7 (1.2–2.5)	0.003
Initial serum bicarbonate concentration (per increase of 3.6 mmol/liter)	1.3 (0.7–2.4)	0.41
Initial partial pressure of arterial carbon dioxide (per decrease of 7.8 mm Hg)	3.4 (1.9–6.3)	<0.001

* In this analysis, the cerebral-edema group was compared with the control group by means of logistic regression. CI denotes confidence interval. To convert the value for serum glucose to millimoles per liter, multiply by 0.056, and to convert the value for serum urea nitrogen to millimoles per liter, multiply by 0.36.

† The increase or decrease used in the analysis of each continuous variable (except age) represents a change of 1 SD in the variable in the control children with diabetic ketoacidosis.

DISCUSSION

In this study, the children with diabetic ketoacidosis who had higher serum urea nitrogen concentrations and more severe hypocapnia at presentation than other children with diabetic ketoacidosis were at increased risk for cerebral edema. Of the therapeutic factors analyzed, only treatment with bicarbonate was associated with cerebral edema. Neither the initial serum glucose concentration nor the rate of change in the serum glucose concentration during therapy was associated with the development of cerebral edema, after adjustment for other covariates; the same was true of the rates of fluid, sodium, and insulin administration.

In the current study, symptomatic cerebral edema occurred in approximately 1 percent of the episodes of diabetic ketoacidosis. Asymptomatic cerebral swelling, however is thought to occur more frequently.[4,21] Whether these conditions represent a spectrum of disease presentation or whether they are manifestations of different pathophysiologic processes is unknown. Equally controversial is whether specific therapies contribute to the development of cerebral edema. In the current study as well as several previous investigations,[8,22,23] symptomatic cerebral edema developed in a few children with diabetic ketoacidosis before the initiation of therapy. This observation suggests that although variations in treatment may exacerbate an ongoing pathologic process, cerebral edema is not necessarily caused by therapeutic interventions.

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.[5,6] In the current study, the differences associated with these three variables were not significant after adjustment for other covariates. The results of our study agree with those of a study in which the initial partial pressure of arterial carbon dioxide was found to be an important predictor of the risk of cerebral edema.[24]

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.[25,29-31] The current data do not fully support this theory, since none of the relevant variables — the serum glucose concentration at presentation, the change in serum glucose concentration during therapy, or the rate of fluid or sodium administration — were associated with the risk of cerebral edema.

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.[24,32] 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.[33] Hyperglycemia superimposed on an ischemic insult increases the extent of neurologic damage, blood–brain barrier dysfunction, and edema formation.[34,35] This interaction might help to explain the occurrence of neurologic damage in association with minor degrees of cerebral hypoperfusion. Blood–brain barrier dysfunction and vasogenic edema may occur several hours after an ischemic insult as a result of the release of vasoactive substances and mediators of inflammation.[34,35] The occurrence of cerebral edema several hours after the initiation of therapy thus correlates well with the hypothesis that the basis of this complication is ischemia. Finally, the more frequent occurrence of cerebral edema in children than in adults may be explained in part by the fact that children's brains have higher oxygen requirements than adults' brains and are thus more susceptible to ischemia.[10,36]

Our study was nonetheless limited in its ability to detect associations of smaller magnitude; in addition, within the 95 percent confidence intervals for the risks associated with several variables were values that indicated associations that were potentially relevant clinically. We therefore cannot definitively conclude that variables that were not associated with cerebral edema in this study are in fact unimportant in its pathogenesis.

We conclude that children with diabetic ketoacidosis who present with high initial serum urea nitrogen concentrations and low partial pressures of arterial carbon dioxide are at increased risk for cerebral edema.. Children with these biochemical features should be monitored

extensively for signs of neurologic deterioration, and hyperosmolar therapy should be available for immediate use in case early signs of cerebral edema occur. Finally, treatment with bicarbonate is associated with an increased risk of cerebral edema and should be avoided in most circumstances.

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