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 61 children who had been hospitalized for diabetic ketoacidosis within a 15-year period and in whom cerebral edema had developed. Two additional groups of children with diabetic ketoacidosis but without cerebral edema were also identified: 181 randomly selected children and 174 children matched to those in the cerebral-edema group with respect to age at presentation, onset of diabetes (established vs. newly diagnosed disease), initial serum glucose concentration, and initial venous pH. Using logistic regression, we compared the three 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; $P=0.003$). A comparison of the children with cerebral edema with those in the matched control group also showed that cerebral edema was associated with lower partial pressures of arterial carbon dioxide and higher serum urea nitrogen concentrations. 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. (N Engl J Med 2001;344:264-9.)

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 developed between 1982 and 1997 at any of 10 pediatric centers. To identify these children, we reviewed the records of all the children who had been admitted because of diabetic ketoacidosis and whose records indicated that they had had cerebral edema, cerebral infarction, coma, seizures, or death, or that they had undergone computed tomographic scanning, magnetic resonance imaging, intubation, or treatment with mannitol. The records of all children who died (with or without type 1 diabetes) at these 10 centers during the study period were also reviewed to ensure that no cases of cerebral edema related to diabetic ketoacidosis had been missed.

To be included in the study, children identified as having cerebral edema were required to meet all the following criteria: the

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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. Six patients whose radiographs revealed patterns of infarction consistent with the consequences of cerebral edema were included in the cerebral-edema group.[9]

Control Groups

For each child with cerebral edema, we identified six other children who were designated as controls, three in each of two control groups. One control group (the "random controls") 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 each center during the study period. The second control group (the matched controls) consisted of children with diabetic ketoacidosis (as defined above) who were matched with the children with cerebral edema according to age (within two years), onset of diabetes (established vs. newly diagnosed disease), venous pH at presentation (within 0.1), and serum glucose concentration at presentation (within 200 mg per deciliter [11.1 mmol per liter]). If pH values were not available, children were matched according to serum bicarbonate concentration (within 3 mmol per liter). If more than three matched controls could be identified for a child with cerebral edema, the controls whose dates of admission most closely approximated that of the child with cerebral edema were chosen.

Data Collection

The following data from the record of each child were recorded by one investigator at each center: 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. In the cerebral-edema group, these rates and changes in biochemical variables during treatment were calculated for the interval between the initiation of therapy (defined as the first intravenous administration of fluids or insulin) and the onset of symptomatic cerebral edema; in the control groups, these values were calculated for the same interval.

To assess interrater agreement in the recording of data, 10 percent of the records were randomly selected and reexamined by a single investigator. Interrater agreement with respect to eight variables (the initial serum glucose and sodium concentrations, the initial venous pH value, the use or nonuse of a bolus dose of insulin, the rates of insulin and fluid administration during the first hour of treatment, the use or nonuse of bicarbonate therapy, and the dose of bicarbonate, if used) was evaluated with use of the weighted kappa statistic. The consistency of the recording of data among investigators was excellent, with a median kappa statistic of 0.9 (range, 0.6 to 1.0).

The study was approved by the institutional review board of each participating institution.

Statistical Analysis

We compared data from the cerebral-edema group with data from both of the control groups by one-way analysis of variance for continuous variables and the chi-square test for categorical variables. The Kruskal–Wallis test was used when variances were unequal among the groups. The Scheffé[15] and Bonferroni[16] procedures were used to adjust for multiple comparisons in the analyses of variance and chi-square tests, respectively.

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. We compared the cerebral-edema group with the matched control group by means of a conditional 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. For continuous data, missing values (12 percent of the continuous data points) were imputed.[17]

Using bootstrap methods, we performed 1000 iterations of the multivariate analyses to assess their stability.[18,19] We considered the association of a variable with cerebral edema to be validated if a significant association with cerebral edema was found in more than 50 percent of the 1000 repeated analyses.[19] All the statistical computations were two-tailed and were performed with Stata statistical software[20] (version 6.0, Stata, College Station, Tex.).

RESULTS

Incidence of Cerebral Edema

Clinically apparent cerebral edema occurred in 61 of 6977 hospitalizations for diabetic ketoacidosis during the study period (0.9 percent; 95 percent confidence interval, 0.7 to 1.1 percent). The diagnosis of cerebral edema was based on deterioration in mental status accompanied by radiographic evidence in 32 of the 61 children (52 percent), by changes in mental status that improved after therapy for suspected cerebral edema in 27 children (44 percent), and by postmortem findings in 2 children (3 percent). Neurologic deterioration occurred a median of 7 hours (range, 0 to 25) after the initiation of therapy for diabetic ketoacidosis (Fig. 1), but in three of the children (5 percent), all of whom had radiographically apparent cerebral edema, it occurred before the initiation of therapy.

Of the 61 children with cerebral edema, 35 (57 percent) recovered without sequelae, 13 (21 percent) survived with permanent neurologic dysfunction, and 13 (21 percent) died. During the study period, only two other children died as a result of diabetic ketoacidosis, both owing to cardiac arrest associated with hypokalemia and hypocalcemia.

Demographic and Initial Biochemical Variables

The 61 children in whom cerebral edema occurred were younger, more likely to be white, and more likely to have newly diagnosed diabetes than the 181 children in the randomly selected control group (Ta-

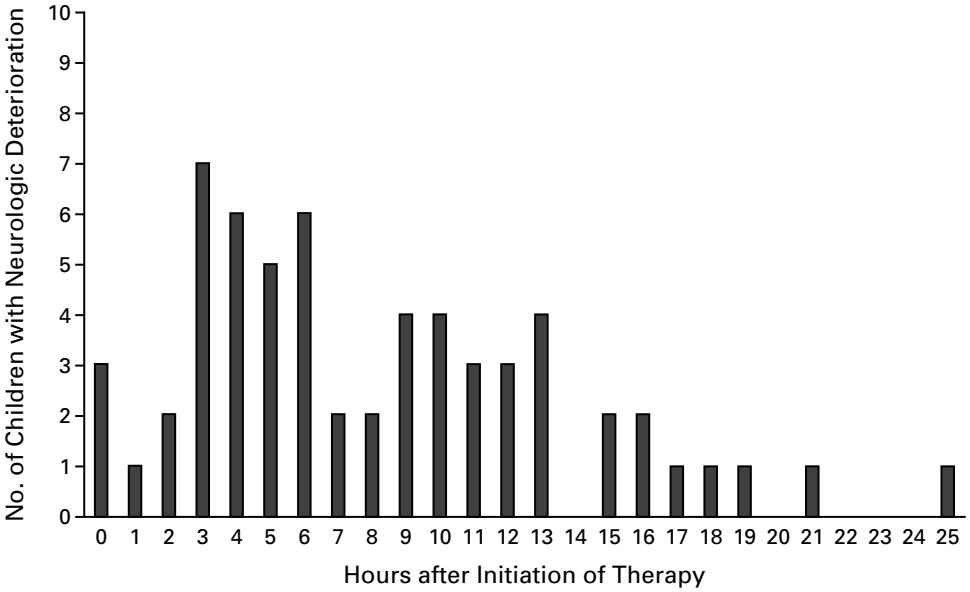

Figure 1. Time between the Initiation of Therapy and Neurologic Deterioration in Children with Diabetic Ketoacidosis and Cerebral Edema.

ble 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 randomly selected controls.

The 61 patients in the cerebral-edema group and the 174 children in the matched control group were well matched: there were no significant differences between these groups with respect to age, the proportion with newly diagnosed diabetes, serum glucose concentrations, and arterial pH values at the time of presentation (Table 1). However, the children with cerebral edema had significantly higher serum urea nitrogen concentrations and significantly lower partial pressures of arterial carbon dioxide than the matched controls. Eighty-five percent of the children in the cerebral-edema group had initial partial pressures of arterial carbon dioxide of less than 18 mm Hg, as compared with 54 percent of the random control group and 69 percent of the matched control group.

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, we excluded the initial serum osmolality values from the multivariate analysis because of collinearity. 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 (data not shown).

Comparison of the Children with Cerebral Edema and the Matched Controls

In the conditional logistic-regression analysis, both a higher serum urea nitrogen concentration and a lower partial pressure of arterial carbon dioxide were independently associated with cerebral edema (Table 3). A smaller increase in the serum sodium concentration during therapy and treatment with bicarbonate were also significantly associated with cerebral edema.

We evaluated the timing of bicarbonate administration in relation to the onset of symptoms of cerebral edema in order to investigate the possibility of bias in bicarbonate administration. We sought to ensure that physicians were not administering bicarbonate in response to deteriorating mental status, thus creating a misleading association between this intervention and cerebral edema. Of the 23 children in the cerebral-edema group who were treated with bicarbonate, only 3 (13 percent) received the first dose within two hours before the onset of neurologic deterioration. By comparison, of the 43 children in the matched control group who were treated with bicarbonate, 4 (9 percent) received their first dose during this interval ($P=0.69$). Thus, no bias in the use of bicarbonate was detected.

TABLE 1. CHARACTERISTICS OF THE CHILDREN AT THE TIME OF PRESENTATION.*

VARIABLE	CHILDREN WITH CEREBRAL EDEMA (N=61)	MATCHED CONTROLS (N=174)	RANDOM CONTROLS (N=181)	P VALUE†
Age (yr)	8.9±4.2	9.0±4.2	11.3±5.0	<0.001
Male sex (%)	57	54	41	0.02
White race (%)	73	67	53	0.009
Newly diagnosed diabetes (%)	66	64	39	<0.001
Serum bicarbonate (mmol/liter)	5.9±2.7	6.5±2.9	7.9±3.6	<0.001
Serum urea nitrogen (mg/dl)	27±14	21±11	20±9	0.002
Serum creatinine (mg/dl)	1.5±1.1	1.3±1.2	1.1±0.7	0.04
Serum glucose (mg/dl)	758±330	700±286	614±244	0.002
Arterial pH‡	7.06±0.10	7.09±0.10	7.12±0.11	<0.001
Partial pressure of arterial carbon dioxide (mm Hg)§	11.3±6.5	15.1±8.4	17.9±7.8	<0.001

*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.

†P values are for the comparison among all three groups. There were no significant differences among the three groups in the following variables at presentation: serum sodium concentration, corrected serum sodium concentration, initial serum potassium concentration, and serum osmolality (data not shown). After adjustment for multiple comparisons by the Scheffé or Bonferroni procedure, there were no significant differences between the cerebral-edema group and the matched control group in any of the variables except the serum urea nitrogen concentration and the partial pressure of arterial carbon dioxide; the cerebral-edema group and the random control group remained significantly different with respect to all the variables.

‡Arterial pH values were calculated according to the following formula[13]: arterial pH = venous pH + 0.05.

§The partial pressures of arterial carbon dioxide were calculated according to the following formula[14]: partial pressure of arterial carbon dioxide = partial pressure of venous carbon dioxide − 6, with all values in millimeters of mercury.

Validation of Multivariate Analyses

With bootstrap analysis, the results of the multivariate regression analyses were validated. All the variables that were found to be associated with cerebral edema in the original analyses were significantly associated with cerebral edema in more than 75 percent of the 1000 iterations of the multivariate analyses.

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. Smaller increases in the serum sodium concentration during therapy also indicated a greater likelihood of 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

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 random 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 randomly selected control children with diabetic ketoacidosis.

TABLE 3. MULTIVARIATE ANALYSIS OF RISK FACTORS FOR CEREBRAL EDEMA IN THE CHILDREN WITH CEREBRAL EDEMA AS COMPARED WITH THE MATCHED CONTROL GROUP.*

VARIABLE†	RELATIVE RISK (95% CI)	P VALUE
Male sex	0.6 (0.3–1.4)	0.27
Age (per 1-yr increase)	0.9 (0.6–1.3)	0.53
Initial serum sodium concentration (per increase of 5.8 mmol/liter)	0.7 (0.5–1.02)	0.06
Initial serum glucose concentration (per increase of 244 mg/dl)	1.4 (0.5–3.9)	0.58
Initial serum urea nitrogen concentration (per increase of 9 mg/dl)	1.8 (1.2–2.7)	0.008
Initial serum bicarbonate concentration (per increase of 3.6 mmol/liter)	1.2 (0.5–2.6)	0.73
Initial partial pressure of arterial carbon dioxide (per decrease of 7.8 mm Hg)	2.7 (1.4–5.1)	0.002
Rate of increase in serum sodium concentration during therapy (per increase of 5.8 mmol/liter/hr)	0.6 (0.4–0.9)	0.01
Rate of decrease in serum glucose concentration during therapy (per decrease of 190 mg/dl/hr)	0.8 (0.5–1.4)	0.41
Rate of increase in serum bicarbonate concentration during therapy (per increase of 3 mmol/liter/hr)	0.8 (0.5–1.1)	0.15
Administration of insulin bolus	0.8 (0.3–2.2)	0.62
Treatment with bicarbonate	4.2 (1.5–12.1)	0.008
Rate of infusion of intravenous fluid (per increase of 5 ml/kg of body weight/hr)	1.1 (0.4–3.0)	0.91
Rate of infusion of sodium (per increase of 0.6 mmol/kg/hr)	1.2 (0.6–2.7)	0.59
Rate of infusion of insulin (per increase of 0.04 unit/kg/hr)	1.2 (0.8–1.8)	0.30

*In this analysis, the cerebral-edema group was compared with the matched control group by means of conditional logistic regression. CI denotes confidence interval. To convert the values 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 randomly selected control children with diabetic ketoacidosis.

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 these studies, however, children with cerebral edema were not compared with controls, and there was no adjustment for possible confounding factors. 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 recent 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]

We found that smaller increases in the serum sodium concentration during therapy were associated with cerebral edema, in agreement with previous studies.[3,5,25,26] The rates of fluid or sodium administration, however, were not associated with the risk of cerebral edema, after adjustment for other covariates. In children with cerebral edema, failure of the serum sodium concentration to rise during therapy may not be the result of excess administration of free water. Physiologic responses to cerebral injury, such as cerebral salt wasting, may alter sodium homeostasis in these children.[27,28]

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 require-

ments than adults' brains and are thus more susceptible to ischemia.[10,36]

Although large in comparison with previous studies, 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. In addition, several children in the cerebral-edema group who met the clinical criteria for cerebral edema did not have radiographic or postmortem documentation of its presence. We cannot be certain that the observed neurologic decompensation in the latter children was due to cerebral edema; however, other causes of their neurologic abnormalities could not be identified, and the results of initial radiographic studies in children with cerebral edema may be normal, despite profound neurologic depression.[6,10] Because data were not available for every variable of potential interest, we also cannot exclude the possibility that confounding factors that were not analyzed may have influenced the detected associations, particularly those related to the use of bicarbonate treatment.

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. In addition, the lack of an increase in the serum sodium concentration during therapy is associated with an increased probability of 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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