

### **DKA-related cerebral edema and intravenous fluid therapy: Potential pitfalls of uncontrolled retrospective studies**

*To the Editor:*

The retrospective analysis of children with diabetic ketoacidosis (DKA) by Hoorn et al<sup>1</sup> compared 12 children with cerebral edema (CE) with 2 control groups without CE. The authors found that the CE group had a decline in effective osmolality during treatment but the control groups did not, and that the CE group received and retained more fluid. They concluded that the drop in effective osmolality may play a causal role in the development of CE.

Clinically apparent CE occurs infrequently during DKA and thus is difficult to study prospectively. However, retrospective study designs carry a substantial risk of bias.<sup>2,3</sup> When evaluating associations, it is essential that patients with CE and controls be matched in terms of illness severity and other important variables, or that differences in these factors are adjusted for in multivariate analyses. Hoorn et al did neither of these. Furthermore, the authors selected 1 control group for hypernatremia during therapy, thereby biasing the analysis by selecting a control group with higher previous probability of having a rise in osmolality.

Hoorn et al documented more fluid administration and retention in the CE group and attributed the osmotic changes to treatment variations. These results are greatly limited by the lack of adjustment for possible confounding variables. The patients with CE were substantially more dehydrated (based on significantly higher blood urea nitrogen concentrations) than the control patients without hypernatremia, explaining why the CE group would have received more fluids. In addition, hypernatremia and hyperosmolality preserve intravascular volume, likely improving peripheral perfusion in hypernatremic control patients and decreasing the fluid administration requirements. Previous studies that used multivariable methods to adjust for baseline differences in DKA severity found no association between fluid administration and CE, despite a lower increase in serum sodium concentration during treatment of DKA in patients with CE.<sup>4</sup>

Finally, there appears to be an error in the reported fluid retention in the CE patients. The authors noted that mean fluid administration was 69 mL/kg in the CE patients, versus 35 and 27 mL/kg in the 2 control groups, and urine output was 64 mL/kg in the CE patients and 23 and 24 mL/kg in the 2 control groups. The authors stated that the CE patients retained 52 mL/kg of fluid, compared with 8 and 3 mL/kg in the controls. With a mean fluid intake of 69 mL/kg and a mean urine output of 64 mL/kg, it seems implausible, if not impossible, that the mean retained fluid volume could have been 52 mL/kg. Using the mean values given, a retained fluid volume of 5 mL/kg seems more likely.

In summary, Hoorn et al suggested that a drop in osmolality during treatment for DKA occurs more often in patients with CE and may play a causal role. However, their analysis lacks some essential adjustments for differences in DKA severity and other factors, calling into question the interpretation of their data. Finally, the authors may have made errors in calculating fluid retention, further challenging the validity of their results.

Nicole Glaser, MD  
Department of Pediatrics

Nathan Kuppermann, MD, MPH  
Department of Emergency Medicine  
University of California Davis School of Medicine  
Sacramento, California  
10.1016/j.jpeds.2007.09.013

### **REFERENCES**

1. Hoorn E, Carlotti A, Costa L, et al. Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. *J Pediatr* 2007;150:467-73.
2. Hayden G, Kramer M, Horwitz R. The case-control study: a practical guide for the clinician. *JAMA* 1982;247:326-31.
3. Rothman KJ, Greenland S. *Modern Epidemiology*. 2<sup>nd</sup> edition. Philadelphia: Lippincott, Williams & Wilkins; 1998.
4. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. *N Engl J Med* 2001; 344:264-9.

### **Cerebral edema in diabetic ketoacidosis with serum sodium <135 mEq/L**

*To the Editor:*

Hoorn et al<sup>1</sup> have compared a group of patients with diabetic ketoacidosis (DKA) and cerebral edema (CE) with 2 control groups without CE, 1 group with and the other group without hypernatremia. Their findings suggest that a gradual decrease in plasma glucose level and a concomitant increase in serum sodium level decrease the likelihood of CE. This finding brings us a little closer to understanding the mechanisms of CE in DKA. However, our analysis of the authors' data reveals a characteristic of the CE group that the authors did not highlight but that may be crucial. The CE group had significantly lower levels of serum sodium at the start of therapy than even the low-sodium control group (LSCG). Their 95% confidence interval (CI) was below the normal serum sodium threshold (135 mEq/L), whereas that of the LSCG was above this threshold.

We have previously shown that patients with DKA have elevated osmolality (measured osmolality evaluated by depression of the freezing point) and a large osmolar gap (osmolar gap = measured osmolality - calculated osmolality; calculated osmolality =  $2 \times P_{Na} + P_{Glucose}$  (in mmol/l)).<sup>2</sup>

Unmeasured substances like ketoacids are responsible for the osmolar gap. Using a modified red blood cell saline fragility test, we previously showed that ketoacids are osmotic in nature and cause fluid shifts across cell membranes.<sup>3</sup> Like glucose, ketoacids also are responsible for effective osmolality in DKA.

Hoorn et al's finding of significant hyponatremia before the onset of treatment in patients with CE concurs with our findings. Patients with DKA and high serum osmolality (due to high levels of glucose [a measured substance] and ketoacids [unmeasured]) will respond with reduced serum sodium levels in an effort to maintain serum osmolality as close to normal as possible. Treatment of DKA produces a drop in glucose and ketoacid levels. Physicians know to use care to decrease glucose levels gradually, but they are not aware of how quickly ketoacid levels can change.

We believe that Hoorn et al have demonstrated that a serum sodium level <135 mEq/L before treatment is a risk factor for the development of CE and may indicate high levels of unmeasured osmotic substances in the blood. Moreover, we reiterate that patients with DKA should have serum osmolality measured objectively by such techniques as the depression of the freezing point, because this provides a clearer index of the changes occurring during the treatment of DKA.<sup>4</sup>

Akatoli Sema, DCH  
Jacob M. Puliylal, MD, MRCP, MPhil  
Department of Pediatrics  
St Stephens Hospital  
Delhi, India  
10.1016/j.jpeds.2007.09.017

## REFERENCES

1. Hoorn EJ, Carlotti AP, Costa LA, MacMohan B, Bohn G, Zietse R, et al. Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. *J Pediatr* 2007;150:467-73.
2. Puliylal J, Puliylal M, Hincliff R. Hypertonicity in diabetic ketoacidosis: unexpected biochemical correlates and clinical implications. Presented at the Joint Meeting of the International Symposium on Diabetes and Endocrine Disorders of the Young and the 4th Asian Symposium of Childhood and Juvenile Diabetes, Chaing Mai, Thailand, January 6-9, 1997.
3. Puliylal JM. Osmotonicity of acetoacetate: possible implications for cerebral edema in diabetic ketoacidosis. *Med Sci Monit* 2003;9:BR130-3.
4. Puliylal JM, Bhambhani V. Ketoacid levels may alter osmotonicity in diabetic ketoacidosis and precipitate cerebral edema [letter]. *Arch Dis Child* 2003;88:366.

## Treatment of diabetic ketoacidosis and the risk of cerebral edema

*"For every complex problem there is an answer that is clear, simple, and wrong." — H.I. Mencken*

*To the Editor:*

The osmolar hypothesis for the development of cerebral edema (CE) in pediatric diabetic ketoacidosis (DKA) is as attractive for its clarity and simplicity as it has been difficult to substantiate.<sup>1</sup> Hoorn et al<sup>2</sup> proposed that preventing a drop in effective plasma osmolality will minimize the likelihood of

CE. Their retrospective analysis involved 7 patients treated in the intensive care unit at Toronto's Hospital for Sick Children between 1994 and 1999 and 5 patients seen at the University Hospital of São Paulo between 1996 and 2005. They found that, compared with a group of 44 controls with hyponatremia and a group of 13 controls without hyponatremia, effective osmolality decreased only in those who developed CE, and that the CE group received more near-isotonic fluids.

This study fails to implicate injudicious fluid replacement therapy as causal, because it is not a true case-control study. The risk of CE is associated with younger age, new-onset diabetes, and greater severity of dehydration and acidosis, factors that must be controlled when analyzing the effect of treatment on the development of CE. In a multicenter study, the location of treatment also should be controlled, and in a study spanning many years that can include changes in treatment protocol, time of treatment needs to be controlled as well. None of this was done in the study of Hoorn et al.

Two earlier investigations attempted true case control. The landmark study of Glaser et al<sup>3</sup> compared each of 61 patients with CE from 10 reporting centers with 3 random controls and 3 controls matched for age, established or new-onset diabetes, pH, and serum glucose concentration. The only therapeutic variable associated with risk of CE risk was administration of bicarbonate. There was no association with the tonicity or volume of fluids or with the rate of glucose decline. In another study, Muir et al<sup>4</sup> matched 26 CE cases with 62 controls on the basis of age, osmolality, and CO<sub>2</sub> concentration and found that the rate of fluid administration was nearly identical in the period before onset of CE. These 2 studies demonstrate that when the severity of presentation is controlled for, there is no evidence for administration of greater fluid volumes in those who develop CE.

The most interesting comparison is with a study that also drew from the Canadian population but covered the 2 years subsequent to the sample of Hoorn et al (1991-2001) and was not confined to patients hospitalized in the Toronto center.<sup>5</sup> A total of 21 cases were identified and matched only for treating institution with 2 controls each. Notably, 20% of the cases of CE developed before the start of treatment. When correction was made for the degree of dehydration, there was no significant difference in fluid volume administered to those who developed CE, and the rise in serum sodium concentration with treatment was actually greater in the cases than in the controls. Hoorn et al did not address these contradictory observations from a larger and comparably controlled population-based series.

Another study that they did not discuss, a case-control study from the UK, yielded findings similar to theirs. In that study, 43 cases were matched with 169 controls for age, sex, established or newly diagnosed diabetes, and date of admission, but not for the severity of presentation. The early administration of insulin and high volumes of fluid in the first hours were found to be risk factors for CE. The authors