What are risk factors for cerebral edema in children with DKA?

Glaser et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med 2001;344:264-9.

Take Home Message: Children with diabetic ketoacidosis who have low partial pressures of carbon dioxide and high serum urea nitrogen concentrations at presentation, and those who are treated with bicarbonate, are at increased risk for cerebral edema.

Highlights: It has been controversial why some children with diabetic ketoacidosis (DKA) develop cerebral edema and whether any therapies contribute to its development. Prior studies investigating risk factors for cerebral edema did not use controls without cerebral edema. In 2001, Glaser et al.[i] performed a case control study comparing 61 children who had DKA and developed cerebral edema to 6 controls per case (3 random controls, 3 matched for multiple baseline characteristics). They found that children with DKA who had higher serum urea nitrogen concentrations and lower partial pressure of carbon dioxide at presentation were more likely to develop cerebral edema. Additionally, the administration of bicarbonate was the only therapeutic intervention which was found to increase the risk for cerebral edema. The lack of an increase in sodium concentration during treatment was also associated with an increased risk of cerebral edema.

Factors that have been implicated with cerebral edema in past studies, such as younger age, a new diagnosis of diabetes, initial serum glucose concentration, rate of change of serum glucose concentration, rate of fluid administration, and rate of insulin administration, were not found to be associated with cerebral edema in this study.

The authors hypothesize that the development of cerebral edema may be, in part, related to brain ischemia, as hypocapnia can cause cerebral vasoconstriction and dehydration can decrease brain perfusion.

The Nitty-Gritty:

- **Design:**
    - Case-control study
    - Subjects
        - Cerebral edema group (n=61)
        - Randomly selected control group (n=181)
        - Matched control group (n=174)
    - Setting: 10 university pediatric centers (9 in US, 1 in Australia)
    - Study period: 1982-1997
    - Method: children in whom cerebral edema related to DKA developed were compared to randomly selected controls with DKA and controls with DKA matched for age at presentation, onset of diabetes, initial serum glucose concentration, and initial venous pH.

    The three groups were compared with respect to demographic characteristics, biochemical varbiables at time of presentation. The matched groups were compared with respect to therapeutic interventions and changes in biochemical values during treatment

- Analysis: logistic regression

- **Population:**

  - **Inclusion Criteria for cerebral edema group:**

    - Identified as having cerebral edema

    - Presence of DKA (defined as serum glucose >300 mg/dl, venous pH < 7.25, or a serum bicarbonate concentration <15mmol/, and the presence of ketones in the urine

    - Alteration in mental status

    - Either radiographically or pathologically confirmed cerebral edema

- **Results:**

  - **Incidence of cerebral edema:** 0.9% (61/6977), 95% CI 0.7-1.1%

    - 57% recovered without sequelae

    - 21% survived with permanent neurologic dysfunction

    - 21% died

  - **Demographic and Initial Biochemical Variables**: comparisons are cerebral edema group vs. random controls (variables were not significantly different between cerebral edema group and matched control group except the cerebral edema group had

significantly higher serum urea nitrogen concentrations and significantly lower partial pressures of arterial carbon dioxide. For those variables, the comparisons are cerebral edema group vs. matched controls vs. random controls

- § Age (yr): 8.9±4.2 vs. 11.3±5.0 (P<0.001)
- § Male sex (%): 57 vs. 41 (P=0.02)
- § White race (%) 73 vs. 53 {P=0.009)
- § Newly diagnosed diabetes (%): 66 vs. 39% (P <0.001)
- § Serum bicarbonate (mmol/L): 5.9±2.7 vs. 7.9±3.6 (P<0.001)
- § Serum urea nitrogen (mg/dl): 27±14 vs. 21±11 vs. 20±9 (P=0.002)
- § Serum creatinine (mg/dl): 1.5±1.1 vs. 1.1±0.7 (P=0.04)
- § Serum glucose (mg/dl): 758±330 vs. 614±244 (P=0.002)
- § Arterial pH: 7.06±0.10 vs. 7.12±0.11 (P<0.001)
- § Partial pressure of arterial carbon dioxide: 11.3±6.5 vs. 15.1±8.4 vs. 17.9±7.8 (P<0.001)

- o **Cerebral edema group vs. Random controls – multivariate analysis of risk factors**
  - § Male sex: RR 0.9 (95% CI 0.4-1.8), P=0.68

§ New onset of diabetes: RR 1.3 (95%CI 0.5-3.1) P=0.57

§ Age (per 1-yr increase): RR 0.9 (95% CI 0.9-1.0)P=0.20

§ Initial serum sodium concentration (per increase of 5.8 mmol/L): RR 0.8 (95% CI 0.6-1.1) P=0.19

§ Initial serum glucose concentration (per increase of 244 mg/dl): RR 1.0 (95% CI 0.7-1.5) P=0.98

§ *Initial serum urea nitrogen concentration (per increase of 9 mg/dl): RR 1.7 (95% CI 1.2-2.5) P=0.003*

§ Initial serum bicarbonate concentration (per increase of 3.6 mmol/liter): RR 1.3 (95% CI 0.7-2.4) P=0.41

§ *Initial partial pressure of arterial carbon dioxide (per decrease of 7.8 mm Hg): RR 3.4 (95% CI 1.9-6.3) P<0.001*

- **Cerebral edema group vs. Matched controls – multivariate analysis of risk factors**

§ *Initial serum urea nitrogen concentration (per increase of 9 mg/dl): RR 1.8 (95%CI 1.2-2.7) P=0.008*

§ *Initial partial pressure of arterial carbon dioxide (per decrease of 7.8 mm Hg): RR 2.7 (95%CI 1.4-5.1) P=0.002*

§ *Rate of increase in serum sodium concentration during therapy (per increase of 5.8 mmol/liter/hr): RR 0.6 (95% CI 0.4-0.9): P=0.001*

§ Rate of decrease in serum glucose concentration during therapy (per decrease of 190 mg/dl/hr): RR 0.8 (0.5-1.4) P=0.41

§ Rate of increase in serum bicarbonate concentration during therapy (per increase of 3 mmol/liter/hr): RR 0.8 (95%CI 0.5-1.1) P=0.15

§ Administration of insulin bolus: RR 0.8 (95%CI 0.3-2.2) P=0.62

§ *Treatment with bicarbonate: RR 4.2 (95%CI 1.5-12.1) P=0.008*

§ Rate of infusion of intravenous fluid (per increase of 5 ml/kg of body weight/hr): RR 1.1 (95% CI 0.4-3.0) P=0.91

§ Rate of infusion of sodium (per increase of 0.6 mmol/kg/hr): RR 1.2 (95%CI 0.6-2.7) P=0.59

§ Rate of infusion of insulin (per increase of 0.4 unit/kg/hr): RR 1.2 (95% CI 0.8-1.8) P=0.30

- **Criticisms**

o Corrections were made to blood pH and partial pressure of CO2 to account for some being venous and some being arterial [ii]

o There are no details regarding indications for bicarbonate treatment in the patients ii

o No identification of risk factors for death or permanent neurologic sequelae[iii]

[i] Glaser et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med 2001;344:264-9.

[ii] Dunger and Edge. Predicting cerebral edema during diabetic ketoacidosis. N Engl J Med 2001; 344:302-303.

[iii] Gebara BM. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med 2001; 344: 1556.