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Clinical Review

EMERGENCY MEDICINE MYTHS: CEREBRAL EDEMA IN PEDIATRIC DIABETIC KETOACIDOSIS AND INTRAVENOUS FLUIDS

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□ **Abstract—Background: Pediatric diabetic ketoacidosis (DKA) is a disease associated with several complications that can be severe. One complication includes cerebral edema (CE), and patients may experience significant morbidity with this disease. Objective: This review evaluates the myths concerning CE in pediatric DKA including mechanism, presentation of edema, clinical assessment of dehydration, and association with intravenous (i.v.) fluids. Discussion: Multiple complications may occur in pediatric DKA. CE occurs in < 1% of pediatric DKA cases, though morbidity and mortality are severe without treatment. Several myths surround this disease. Subclinical CE is likely present in many patients with pediatric DKA, though severe disease is rare. A multitude of mechanisms likely account for development of CE, including vasogenic and cytotoxic causes. Clinical dehydration is difficult to assess. Literature has evaluated the association of fluid infusion with the development of CE, but most studies are retrospective, with no comparator groups. The few studies with comparisons suggest fluid infusion is not associated with DKA. Rather, the severity of DKA with higher blood urea nitrogen and greater acidosis contribute to CE. Multiple strategies for fluid replacement exist. A bolus of 10 mL/kg of i.v. fluid is likely safe, which can be repeated if hemodynamic status does not improve. Conclusions: Pediatric CE in DKA is rare but severe. Multiple mechanisms result in this disease, and many patients experience subclinical CE. Intravenous fluids are likely not associated with development of CE, and 10-mL/kg or 20-mL/kg i.v. bolus is safe. Published by Elsevier Inc.**

□ **Keywords—cerebral edema; dehydration; diabetic ketoacidosis; fluid infusion; pediatric**

INTRODUCTION

Diabetes mellitus is a common chronic disease among children, with increasing frequency in type 1 and 2 diabetes (1–5). One complication is diabetic ketoacidosis (DKA), which has an incidence of 25% in known type 1 diabetics (3–8). Close to one-third of patients at the time of initial diagnosis of diabetes have DKA, and children younger than 5 years or age are at high risk for DKA (3–7). Other risk factors for DKA at the time of diagnosis include ethnic minority, smaller body mass index, delayed treatment, infectious trigger, and lack of health insurance (1,2,8). Though most commonly occurring in type 1 diabetics, patients with type 2 diabetes can also experience DKA, as 5–25% of patients with type 2 diabetes are in DKA at time of diagnosis (4,8,9). The most common cause is insulin omission, though infection is another common trigger (1,2).

Pediatric DKA is demonstrated by hyperglycemia (serum glucose > 200 mg/dL), anion gap metabolic acidosis, and ketonemia (1,10–14). Disease develops

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absolute or relative deficiency in insulin and excess counterregulatory hormones, resulting in dehydration and electrolyte abnormalities. The mainstay of treatment for these patients includes rehydration with fluids, insulin, and potentially potassium repletion (10–14). One major complication is cerebral edema.

Cerebral Edema

Cerebral edema (CE) is clinically apparent and life threatening in 0.5–1% of patients with DKA (2,14–17). Though the mortality of DKA is < 1%, CE accounts for a significant proportion of these deaths due to brain herniation, which can occur prior to initiation of treatment (15,17). Mortality ranges from 20–90%, with one-fourth of survivors suffering permanent neurologic deficits (1,2,14–16,18). However, CE may be asymptomatic or subtle, with minor mental status changes, which can appear in many cases of pediatric DKA (19–22). This severe complication presents most commonly within the first 7 h of treatment (66%), with 33% presenting 10–24 h after initiation of treatment in type 1 and type 2 diabetics (15,16,23–25).

The diagnosis is clinical, as approximately 40% of patients with CE display normal neuroimaging (1,2,22,26,27). However, diagnosis can be difficult, depending on the presentation. Muir et al. published several criteria for diagnosing cerebral edema, consisting of diagnostic criteria, major criteria, and minor criteria; this is demonstrated in Table 1 (26). A significant consideration is close evaluation of patient neurologic status, with frequent reassessments during management. If suspected or diagnosed, mannitol is the most common first-line therapy at 1 g/kg i.v., though hypertonic saline (3%) is an option at 5–10 mL/kg i.v. (1,2,10–13).

This review will evaluate the literature concerning CE in pediatric DKA, specifically the presentation, underlying mechanism, and potential association with fluid infusion. Authors conducted a search of Google Scholar, PubMed, Google FOAM, and Medline. We sought randomized trials, case controls, case series, and chart reviews that compared groups including patients with DKA and CE and those in DKA with no CE. Much of the literature is relegated to descriptive studies that lack comparator groups. Few randomized studies are available, with the majority including case control and case series (27,28).

Table 1. DKA Diagnostic Criteria (26)

Pediatric DKA Cerebral Edema Diagnostic Criteria
Diagnostic Criteria: abnormal motor or verbal response to pain, decorticate or decerebrate posture, cranial nerve palsy, abnormal neurologic respiratory pattern
Major Criteria: altered mentation/fluctuating level of consciousness, heart rate decelerations (more than 20 beats/min) not improved with hydration or sleep, age-inappropriate incontinence
Minor Criteria: vomiting, headache, lethargy or difficulty arousing from sleep, diastolic blood pressure > 90 mm Hg, age < 5 years
Diagnosis: 1 diagnostic criterion, 2 major criteria, or 1 major and 2 minor criteria
*Sensitivity 92% and Specificity 96%

DKA = diabetic ketoacidosis.

DISCUSSION

A great deal of literature has examined risk factors for the development of CE, with the goal of predicting patients at greater risk for CE. Since the first description of this disease in 1936, a great deal of study has focused on eliciting the cause of CE, means of prevention, and treatment (29). However, CE in pediatric DKA is still a mysterious disease. To evaluate the association of i.v. fluid and CE, first we must evaluate the clinical spectrum of CE and the proposed mechanism, as well as the clinical assessment of dehydration in these patients and management of DKA.

Myth: Cerebral Edema in Pediatric DKA is Rare and Always Clinically Apparent

CE in pediatric DKA that is clinically overt with marked neurologic change is infrequent (20–23,30). Subtle edema occurs in the majority of patients with DKA, as studies using neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI]) in children with DKA have demonstrated the presence of edema before treatment is initiated and during therapy (14,15,23,31,32). Patients who have abnormal mental status during treatment are likelier to possess subtle CE, defined by cerebral ventricle narrowing, than those with normal neurologic status during treatment (33). Any abnormal neurologic assessment, including abnormal Glasgow Coma Scale score (GCS), is associated with higher frequency of MRI changes (16,22,26,33). Krane et al. found edema on head CT in 6 patients treated for DKA, though none of these patients experienced clinically evident signs of the disease (22). Cerebral edema is not rare in pediatric DKA, but the severe form likely represents the extreme representation of a disease spectrum.

Bottom Line: Cerebral edema occurs along a spectrum in pediatric DKA and is likely more common than originally thought. However, the form of edema that results in herniation is likely rare.

Myth: The Mechanism of Cerebral Edema is Predominantly Due to Rapid Osmotic Changes with Treatment

Many published treatment recommendations for pediatric DKA attempt to minimize the risk of CE, and providers