

Portending Complications in Pediatric Diabetic Ketoacidosis

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Diabetic ketoacidosis (DKA) is a medical emergency requiring careful titration of fluids and insulin with meticulous monitoring in order to avoid complications. Unlike the West, children in low- and middle-income countries with poor socioeconomic status, malnutrition, sepsis, poor adherence to insulin, alternative medicine use, and inadequate treatment at first-contact healthcare facility, are at increased risk for severe and complicated DKA. The two important complications are cerebral edema (CE) and acute kidney injury (AKI). In this issue, the authors report a retrospective study on the clinical profile and predictors of complications encountered in children with DKA.

Cerebral edema is a serious complication and a major contributor to DKA-related deaths.^{1,2} The diagnosis of CE is based on alteration in mental status (obtundation or disorientation) and either radiographically or pathologically confirmed CE or specific treatment for CE (hyperosmolar therapy or controlled hyperventilation) that was followed by clinical improvement. Glaser et al. showed that CE occurred in 1% of children with DKA, with a mortality rate of 21% and neurologic sequelae in another 21% of patients.^{2,3} About half of the children with DKA had CE on magnetic resonance imaging (MRI) of the brain.³ The prevalence was similar in the Pediatric Emergency Care Applied Research Network (PECARN) DKA FLUID Study, where a clinically apparent brain injury occurred in 0.9% while a decline in mental status Glasgow coma scale scores of <14 (on two consecutive occasions) occurred in 3.5% of children with DKA.⁴

Children have a higher incidence of symptomatic CE as compared to adults, particularly in those with new-onset diabetes. Any child with deterioration in the level of consciousness in spite of improved metabolic state usually indicates CE. Since routine use of MRI is not needed and/or not available in many centers, only clinical criteria are relied upon for diagnosing and managing CE. Muir et al. used the diagnostic criteria for CE that include abnormal response to pain, decorticate and decerebrate posturing, cranial nerve palsies, abnormal central nervous system and respiratory patterns, fluctuating level of consciousness, sustained heart rate deceleration, incontinence, and more nonspecific criteria, such as vomiting, headache, lethargy, and elevated diastolic blood pressure.⁵ In the present study, the authors report a very high number of children with CE (22%). This disproportionately high occurrence may be related to nonspecific clinical signs that could have led to overdiagnosis or due to a higher proportion of severe DKA in which acidosis and hypovolemia per se could lead to alteration in consciousness superadded by sepsis.

The two hits postulated to cause CE include the first hit that occurs before DKA therapy is initiated wherein the dehydration and cerebral hypoperfusion cause ischemia-related cerebral injury. The second hit occurs after fluid therapy is started and is due to

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reperfusion injury.^{6–8} Idiogenic osmoles generated in the brain cells, in the early stages of DKA, protect them against intracellular dehydration and shrinkage. However, during therapy, a rapid decrease in extracellular osmolality favors intracellular fluid shift and the development of CE. This may be secondary to a rapid reduction of blood glucose, excessive fluid replacement, and bicarbonate use.⁹ In the retrospective study by Glaser et al., children with higher serum urea nitrogen, severe hypocapnia at presentation, and treatment with bicarbonate were at increased risk for CE.² Concerns about the role of overaggressive or hypotonic fluid resuscitation as a cause of CE have been raised in the past but neither fluid rate nor type showed any difference in CE.⁴ The present study also found higher urea, higher corrected sodium, and lower serum bicarbonate as independent predictors of CE similar to other reports. Studies have found that a high incidence of CE at the initiation of therapy tends to worsen during the course of treatment. A high index of suspicion for CE is therefore needed, and it may be too late to react at the time of profound neurological depression and respiratory arrest.

Acute kidney injury is another potential complication encountered during DKA management. The reported prevalence of AKI in patients with DKA has been quite variable owing to differences in the population studied, disease severity, and definitions used across studies. In a retrospective study from Canada by Hursh et al., AKI was seen in 64.2% of children hospitalized for DKA (based on the KDIGO criteria) and found volume depletion and severe acidosis associated with AKI.¹⁰ This was consistent with studies from East Asia by Huang et al. and SPinK trial from India by Williams et al., where AKI was present in over a half of DKA episodes at the time of admission.^{11,12} The largest cohort study to date was a secondary analysis of data from the PECARN DKA FLUID study in which AKI occurred in 584/1,359 DKA episodes (43%).¹³

The cause of AKI in DKA is largely prerenal and resolves with adequate hydration. However, if acidosis is severe and prolonged

or when associated with sepsis, it can progress to acute tubular injury. Studies have shown the association of higher initial serum urea nitrogen, higher heart rate, higher glucose-corrected sodium and glucose concentrations, and lower pH with AKI.^{11,13,14} In the present study, the authors found older age, presence of infection, and worse biochemical profile at presentation (lower pH, higher blood glucose, higher lactate, higher corrected sodium, and hyperchloremia) to be associated with AKI. These are quite similar to other studies reiterating the fact that volume depletion at the time of presentation is an important contributor to AKI. However, the problem in DKA like in any other hyperosmolar state is that the clinical assessment of dehydration may not be accurate at presentation. Evidence is evolving to stress on using biochemical markers to assess the severity of dehydration. From a diagnostic perspective, implementing a kidney injury marker into clinical practice, compared with the current kidney function-based approach remains a priority. More research is needed on incorporating biomarkers either as a single-point measure or as a serial trend to diagnose persistent AKI.¹⁴ Thus, to mitigate progression, early identification and appropriate fluid resuscitation are crucial. The use of balanced fluids in DKA to mitigate hyperchloremic acidosis and AKI is being investigated in clinical trials.^{12,15,16}

Clinicians are aware that CE and AKI are still major contributors to mortality and morbidity in children with DKA. Unfortunately, evidence is still weak and more research is needed from large studies with adequate sample sizes to identify modifiable factors to prevent these complications. Early diagnosis with severity classification, appropriate assessment and correction of dehydration, quick referral to an advanced facility if additional organ support is needed, and good rehabilitation with adequate patient education to prevent recurrence are key measures to reduce morbidity and mortality associated with DKA.

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