RARE COMPLICATIONS OF PEDIATRIC DIABETIC KETOACIDOSIS

Shara R Bialo, Sungeeta Agrawal, Charlotte M Boney, Jose Bernardo Quintos

Abstract

The incidence of type 1 diabetes (T1D) among youth is steadily increasing across the world. Up to a third of pediatric patients with T1D present with diabetic ketoacidosis, a diagnosis that continues to be the leading cause of death in this population. Cerebral edema is the most common rare complication of diabetic ketoacidosis in children. Accordingly, treatment and outcome measures of cerebral edema are vastly researched and the pathophysiology is recently the subject of much debate. Nevertheless, cerebral edema is not the only sequela of diabetic ketoacidosis that warrants close monitoring. The medical literature details various other complications in children with diabetic ketoacidosis, including hypercoagulability leading to stroke and deep vein thrombosis, rhabdomyolysis, pulmonary and gastrointestinal complications, and long-term memory dysfunction. We review the pathophysiology, reported cases, management, and outcomes of each of these rare complications in children. As the incidence of T1D continues to rise, practitioners will care for an increasing number of pediatric patients with diabetic ketoacidosis and should be aware of the various systems that may be affected in both the acute and chronic setting.

Key words: Type 1 diabetes; Diabetic ketoacidosis; Complications; Pediatric; Review

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INTRODUCTION

Approximately 1 in 300 youth have type 1 diabetes (T1D)[1], and the incidence in the pediatric population is...
increasing by almost 3% each year in the United States and worldwide. Despite the burgeoning statistics and awareness, the prevalence of diabetic ketoacidosis (DKA) remains as high as 30% in children presenting with T1D. DKA is defined by the American Diabetes Association, the European Society for Paediatric Endocrinology, and the Pediatric Endocrine Society as hyperglycemia (plasma glucose > 200 mg/dL or approximately 11 mmol/L) and venous pH < 7.3 and/or bicarbonate < 15 mmol/L. DKA is the most common cause of death in children with T1D, and the most common rare and primary fatal complication of DKA is cerebral edema. The treatment and prevention of cerebral edema is, therefore, the subject of extensive medical research and attention. However, cerebral edema is not the only complication of DKA worthy of close monitoring during patient care. In this review article, we will examine cerebral edema as well as the vascular, musculoskeletal, pulmonary, gastrointestinal, and cognitive complications of pediatric DKA, which are less common but can result in acute and long-term morbidity.

CEREBRAL EDEMA

Many children who present with DKA have some degree of altered mental status. Typically the altered status is due to acidosis or hyperosmolarity, although some studies show that subclinical cerebral edema occurs in the majority of patients in DKA. Approximately 0.5%-1% of children in DKA develop frank cerebral edema. Morbidity related to cerebral edema is approximately 13%-35% and mortality 24%-28%. Risk factors for the development of cerebral edema during DKA include new onset T1DM, low bicarbonate, low partial pressure of CO₂, high BUN, and high blood glucose.

Conventional thinking attributes the mechanism of injury in cerebral edema to swelling from an influx of fluid into the brain. This influx is thought to be due to the rapidly declining serum osmolarity caused by overly aggressive fluid resuscitation; however, data reveals the only treatment-related risk factor to be administration of bicarbonate. The association between high fluid infusion rates and development of cerebral edema trends toward, but does not reach, statistical significance. The association between high fluid infusion rates and development of cerebral edema trends toward, but does not reach, statistical significance. Radiographic confirmation of cerebral edema in patients with DKA prior to initiation of fluid therapy further discredits the association. Also, many children have normal brain imaging at the onset of clinical cerebral edema and do not develop radiographic signs of edema until hours or days later, suggesting that edema is a consequence rather than the cause of injury.

A more plausible hypothesis is that cerebral edema is caused by cerebral hypoperfusion, which leads to cytotoxic edema (cell swelling and death) at presentation followed by vasogenic edema (breakdown of the blood brain barrier leading to capillary leakage) during treatment. There is supporting evidence for this mechanism, including the association between cerebral hypoperfusion and the risk factors associated with the development of cerebral edema, including high BUN, low bicarbonate, and low partial pressure of CO₂. Additionally, Lam et al. show that untreated DKA in rats is associated with changes on diffusion-weighted Imaging Magnetic Resonance (DWI MR) consistent with cytotoxic edema. When the DKA is treated, the DWI MR images demonstrate slight changes that suggest advancement to vasogenic cerebral edema. MR DWI changes consistent with vasogenic edema have also been shown in children during treatment of DKA. These studies support the model that DKA-related cerebral edema stems from early ischemic brain damage followed by reperfusion injury during treatment.

COAGULOPATHIC COMPLICATIONS

Abnormalities of hemostasis have been identified in patients with poorly controlled diabetes, although the mechanism is not entirely understood. Likewise, clinical studies of both adult and pediatric patients with T1D with DKA have described a variety of transient changes in coagulation factors, such as increased platelet activation, fibrinolytic activity, and endothelial activation. A prospective study of adolescents with T1D and DKA demonstrated low levels of free protein S, which facilitates activated protein C in inactivating von Willebrand factor. Accordingly, the levels of von Willebrand factor activity were increased. Protein C activity was decreased in DKA but normalized following treatment.

DKA is also characterized by elevated levels of inflammatory markers (CRP), cytokines (IL6, IL1beta, TNF alpha), and complement activation. This inflammatory state, combined with the disruption of the normal coagulation cascade, can place patients at increased risk of thrombosis and stroke during acute episodes of DKA.

Deep vein thrombosis

Deep vein thrombosis (DVT) is not uncommon in critically ill children who require central venous catheter placement as they introduce a foreign body, cause endothelial damage, and impaire blood flow. Children and adolescents with DKA, however, appear to be at increased risk of DVT when they undergo placement of a central venous catheter. This increased risk of thrombosis likely stems from shock compounded by DKA, as severe dehydration activates the coagulation cascade and causes venous stasis and DKA itself confers a hypercoagulable state. Gutierrez et al. published the first report to describe this observation in a retrospective case-matched control series. It details that 4 of 8 children with DKA who underwent placement of a femoral central venous catheter developed DVT compared to 0 of the 16 of control patients who underwent central venous catheter placement without diabetes or DKA. A retrospective cohort study published by Worly et al. found similar observations with evidence of femoral
DVT on Doppler ultrasound within 48 h of the central catheter placement for treatment of DKA. Patients in that series with DKA and DVT had significantly higher serum glucose, corrected sodium concentrations, and lower pH and serum bicarbonate than their age-matched cohorts with shock and central venous catheters. DVT in children with DKA and catheter placement is also more common in those less than 3 years of age, which may be due to smaller vessel diameter and greater severity of illness at presentation.[28]

Children with DKA and DVT require low-molecular weight heparin until ultrasound confirmation of DVT resolution, which can take up to 6 mo.[27]. Given the increased risk of DVT and associated morbidity, use of central venous catheters should be avoided in children with DKA when possible. If placement is required, the central venous catheters should be removed as soon as possible and use of prophylactic anticoagulation therapy should be considered in cases of prolonged use.

Cerebral venous thrombosis
In general, the incidence of cerebral sinovenous thrombosis is 0.67 cases per 100000 children per year.[29]. Central venous thrombosis in association with pediatric DKA is reported twice in the medical literature.[29,30]. The first published case report is a 5-year-old girl with known T1D who presented with emesis, lethargy, and mild DKA who then neurologically decompensated 12 h into treatment, as evidenced by unconsciousness, response to painful stimuli only and limb rigidity.[29]. A CT scan demonstrated a thrombosis in the straight sinus and the vein of Galen with ischemic changes in the thalamus. She was anticoagulated with Heparin for 48 h followed by Warfarin for three months, and her baseline neurological status two years later was remarkably normal aside from mild learning difficulties.

The second case reported was in an 8 years old boy on first presentation of T1D with severe DKA with hyperosmolar state with serum glucose of 1668 mg/dL.[30]. Two hours into treatment he became unconscious and with sluggish pupillary response. A CT demonstrated thrombosis in the superior sagittal sinus and vein of Galen, as well as large infarctions in both cerebral hemispheres. Long-term follow-up information is not available for this case.

Stroke
The overall incidence of pediatric stroke is estimated at 2-13 per 100000 children.[31]. Hemorrhagic or ischemic brain infarction accounts for approximately 10% of intracerebral complications of DKA, and not all cases of stroke in DKA are associated with cerebral edema.[32]. The procoagulant state of DKA places patients at increased risk of ischemic brain injury as well as subsequent hemorrhagic conversion arising from hypoxia and vascular injury.[33]. Diagnosis of stroke during an episode of acute DKA is difficult as there is considerable overlap of signs, symptoms, and laboratory data.[33]. Early signs and symptoms of CNS injury include nonspecific findings such as headache, confusion, lethargy, and unexpected changes in heart rate, respiratory rate, or blood pressure.[34]. Focal neurological signs allow clinicians to rapidly identify stroke victims; however, less than 30% of patients with DKA-associated stroke have characteristic focal neurologic deficits.[34]. It is also often difficult to differentiate whether cerebral edema in DKA is the cause or the effect of acute cerebral infarction, as stroke itself may cause cerebral edema. Arterial ischemic and hemorrhagic strokes have been documented in children and youth with DKA in a wide variety of cerebral locations, including single or multiple infarctions or thrombi over unilateral or bilateral lobes. The pathologic tissue findings of acute cerebral infarction related to DKA are not expected to be different from those of a nondiabetic child who has suffered a stroke.

Management and outcomes of pediatric stroke associated with DKA
Treatment guidelines for children and adults with diabetic ketoacidosis and stroke are lacking, including the optimal rehydration rate, parameters for use of thrombolytics and other medications, and monitoring schedules.[35]. In general, pediatric patients with suspected stroke should receive prompt neurological imaging and neurologic consultation while managed in an intensive care setting. Thrombolysis for the treatment of pediatric stroke remains controversial without supportive data, although children have achieved successful outcomes when administered intravenous tissue plasminogen activator for acute treatment of ischemic stroke.[36,37].

The first large-scale prospective outcome study on children with ischemic stroke or sinovenous thrombosis found 41% to have moderate or severe deficits on neurologic examination after a mean of 2.1 years.[38]. A recent cross-sectional outcome study of pediatric patients with ischemic stroke and cerebral sinovenous thrombosis a mean of 10.8 years after onset found that 37% were normal and 15% suffered severe deficits.[39]. The authors found a strong predictor of long-term outcomes to be functional status at 1 year post-stroke.

Few data are available regarding the long-term effects of pediatric stroke secondary to DKA, and the cases available are largely dependent on the anatomic site affected. Foster et al.[24] reviewed the outcomes of 28 case reports of arterial ischemic stroke, cerebral venous thrombotic stroke, and hemorrhagic stroke associated with DKA in youth and noted full recovery in only 14%. The majority of patients were left with varying degrees of residual neurologic deficit and 29% of cases resulted in death or persistent vegetative state. These grim outcomes highlight the need for large, randomized clinical trials of pediatric stroke during DKA treatment in order to help achieve the most positive outcomes.

RHABDOMYOLYSIS
Rhabdomyolysis is the breakdown of skeletal muscle leading to leakage of cell contents and resulting in muscle
pain, weakness, and potential acute renal injury\textsuperscript{[40,41]}. Biochemical changes include elevated creatinine kinase and myoglobinuria. The most common causes of rhabdomyolysis in children are viral myositis, trauma, medications, and underlying metabolic diseases. While rhabdomyolysis is more frequently described in patients with hyperosmolar hyperglycemic syndrome (HHS), it is also a well-documented phenomenon in DKA\textsuperscript{[45]}. Rhabdomyolysis in the setting of diabetes is often subclinical, with risk factors being low pH and high serum glucose, BUN, creatinine, sodium, and osmolality\textsuperscript{[42-45]}. The mechanism by which rhabdomyolysis occurs is unclear, although it is thought to be secondary to the changes in electrolyte and glucose concentration across the muscle cell combined with the presence of insulin\textsuperscript{[42,46,47]}. These changes may lead to increased intracellular calcium which, in turn, can activate proteases and lead to muscle cell leakage.

The incidence of rhabdomyolysis in adults with DKA is approximately 10%\textsuperscript{[43]}. A study of children presenting with new onset T1DM found urine myoglobinuria in 10%\textsuperscript{[44]}. Several case reports detail rhabdomyolysis in pediatric DKA\textsuperscript{[42,44,48,49]}. These patients, who ranged in age from 15 mo to 12 years, all presented with a mixed HH and DKA picture as they had acidosis, a blood glucose > 600 mg/dL, and hyperosmolality. They were also significantly dehydrated with elevated BUN or creatinine, consistent with the risk factors for developing rhabdomyolysis during DKA.

The presence of rhabdomyolysis in adults greatly increases mortality, likely secondary to decreased renal function\textsuperscript{[45]}. While there are no studies looking at the morbidity and mortality of rhabdomyolysis in children presenting in DKA, the incidence of acute renal failure in all children with rhabdomyolysis is 5%\textsuperscript{[46]}. Other serious complications include severe hyperkalemia and hypocalcemia, which can both lead to cardiac arrest\textsuperscript{[50,51]}. Fluid therapy and bicarbonate administration to alkalize the urine are the gold standard treatment to prevent kidney injury.

**PULMONARY COMPLICATIONS**

**Pneumomediastinum**

Pneumomediastinum is a rare event that occurs secondary to alveolar rupture after a change in pressure gradients in the alveoli\textsuperscript{[22]}. These changes can occur secondary to mechanical ventilation, vomiting, coughing, and the valsalva maneuver\textsuperscript{[32,94,95]}. Patients with DKA are at increased risk of developing pneumomediastinum in the presence of emesis and Kussmaul breathing, which can generate alveolar pressures of 20-30 mmHg\textsuperscript{[53-57]}. There are over 50 documented cases of pneumomediastinum in the setting of DKA\textsuperscript{[54,55,56]} and analysis of the series found a male predominance (71% male), an average age of 20 years old, and an average blood glucose of 638 mg/dL\textsuperscript{[58]}. All patients had significant acidosis with respiratory compensation, supporting hyperpnea as a mechanism for the development of pneumomediastinum. Complications include pneumothorax as well as pneumopericardium, which can lead to cardiac tamponade.

Pneumomediastinum classically presents with chest pain and/or dyspnea. Patients often have a positive Hamman’s sign, which is crepitus over the precordium that is synchronized with systole\textsuperscript{[53,59,60]}, and subcutaneous emphysema may also develop. However, many patients are asymptomatic and pneumomediastinum is only found incidentally\textsuperscript{[53,59]}. Additional treatment is not usually required for cases of pneumomediastinum as the leaked air is often reabsorbed without incident\textsuperscript{[53,59]}.  

**Pulmonary edema**

Pulmonary edema is another rare complication of DKA found in both children and adults\textsuperscript{[42,43,62]}. While the edema can be subclinical, some children develop hypoxemia requiring supplemental oxygenation or intubation. To determine the incidence of pulmonary edema in the setting of DKA, Hoffman et al\textsuperscript{[63]} performed CT scans on children on presentation of DKA, 6-8 h into treatment, and on discharge. They found increased pulmonary density on presentation that worsened during treatment and self-resolved by discharge. While none developed hypoxemia, P02 values trended low during treatment in the majority of patients.

The edema is thought to be secondary to a decrease in capillary colloid osmotic pressure during intravenous fluid treatment with 0.45% normal saline\textsuperscript{[41,64,65]}. A concomitant fall in the hematocrit with fall in colloid pressure supports fluid administration rather than increased capillary permeability and leakage as the cause of edema. Hoffman et al\textsuperscript{[63]} also found a negative correlation between lung density and hematocrit, supporting this mechanism.

The development of pulmonary edema in the setting of DKA can be difficult to manage, as it often requires fluid restriction while DKA requires substantial fluid administration to correct total body water losses\textsuperscript{[66]}. Pulmonary edema in pediatric DKA is rare and general outcomes are not well described, although all of the children in case reports recovered without significant pulmonary sequelae\textsuperscript{[44,61,62]}.  

**GASTROINTESTINAL COMPLICATIONS**

**Pancreatitis**

Acute pancreatitis occurs in 2% of children and 11% of adults with DKA\textsuperscript{[66,67]}. It can be difficult to diagnose with concomitant DKA as abdominal pain is a common complaint and non-specific elevation of both lipase and amylase are noted with DKA. Nair et al\textsuperscript{[68]} conducted CT scans on 100 adult patients admitted with DKA and found 11 to have acute pancreatitis, as evidenced by pancreatic enlargement, necrosis, or fluid collections. Elevated serum amylase had a positive predictive value of 69%, elevated lipase 52%, and abdominal pain only 30%.

Haddad et al\textsuperscript{[69]} conducted a prospective study looking at pancreatic enzyme levels of children with new onset
T1DM with and without DKA. Of those with DKA, 40% had elevated amylase and/or lipase levels and 40% had hypertriglyceridemia. Conversely, only 1 of 12 patients (8%) without DKA had mildly elevated lipase. Thirteen percent of patients with DKA had a lipase level that was elevated more than 3 times normal range and reported persistent abdominal pain after the DKA resolved, although their CT scans remained negative. Only one patient’s symptoms recurred with increasing enzyme levels and her repeat imaging was positive for pancreatitis. This study demonstrates that non-specific enzyme elevation is common in children with DKA.

The etiology of non-specific elevation of lipase and amylase during DKA may be secondary to non-pancreatic sources of the enzymes, an insult to the pancreas itself causing enzyme leakage, and decreased renal clearance. In cases of acute pancreatitis during DKA, transient hypertriglyceridemia is postulated to be the primary etiology through both increased blood viscosity and increased levels of free fatty acids in the pancreas secondary to triglyceride lipolysis, ultimately leading to pancreatic ischemia and injury. The child who developed pancreatitis in Haddad’s study did not have hypertriglyceridemia, however, leading the authors to propose that severe acidosis may play a role in the development of acute pancreatitis.

Management of acute pancreatitis during DKA involves aggressive fluid administration, as pancreatitis can worsen intravascular dehydration. Care must be taken when resuming oral intake as it may exacerbate pancreatitis. The cases of pancreatitis described were mild and all resolved without complications.

Upper gastrointestinal bleeding
There is a 9% incidence of upper gastrointestinal (GI) bleeding in adults with DKA, although there are no documented reports in children. The most common manifestation is coffee ground emesis, with hematemesis or melena also noted. Faigel et al conducted a retrospective review of 25 patients who developed upper GI bleeding during DKA; all 8 who underwent endoscopy were found to have esophagitis. Additionally, 63% had esophageal erosions or ulcerations and one (13%) had a Mallory-Weiss tear. Conversely, only 33% of patients with DKA without bleeding had evidence of esophagitis on endoscopy and only 11% had erosions. Acute esophageal necrosis, which is characterized by a black-appearance of the distal esophageal mucosa, is a rare cause of upper GI bleeding in DKA that was not found in Faigel’s study.

Use of ulcer medications, including proton pump inhibitors and H2 receptor antagonists, longer duration of diabetes, and diabetic complications including nephropathy, retinopathy and gastroparesis are clinical risk factors associated with upper GI hemorrhage. Laboratory values associated with an increased risk of hemorrhage include elevated BUN, creatinine, and glucose; arterial pH and coagulation tests did not differ between the two groups. Acute hyperglycemia in particular has been shown to delay gastric emptying, which causes esophageal mucosal damage secondary to acid reflux and ultimately leads to a GI bleed.

Only 32% of those with upper GI bleeding in Faigel’s study underwent endoscopy. While 27% of patients with hemorrhage required blood transfusions, none required invasive therapy and GI bleeding did not directly result in mortality. However, those with GI bleeds had a mortality rate of 15% from other causes, compared to 4% in those without GI bleeds. This higher mortality rate is attributed to greater illness severity with greater likelihood of being admitted to the ICU.

COGNITIVE COMPLICATIONS

Even in the absence of symptoms suggesting cerebral injury, children with diabetic ketoacidosis can exhibit long-term cognitive complications. Ghetti et al assessed for memory deficits in 33 children with T1D who had suffered at least one episode of DKA and 29 children with T1D who had never experienced DKA. Interestingly, the children with DKA history had a significantly lower ability to recall events in association with specific details, as tested by event-color and event-spatial position associations. The average time since the last episode of DKA was 2.54 years, although varied from 0.11 to 14.54 years, and memory performance varied.
was worse in children whose DKA was in the more distant past. This retrospective study also demonstrated that, aside from DKA, reduced memory performance was associated with male sex, young age at onset of diabetes, and severe hypoglycemia. The authors hypothesize that cerebral edema-related hypoxic/ischemic injury to the hippocampus is responsible for these specific, long-term cognitive deficits, as similar outcomes are observed in both clinical and animal studies of hypoxic injury.[83-86]

Animal models allow for a more controlled assessment of DKA-related cognitive dysfunction. Rats with streptozotocin-induced diabetes who are subjected to only one episode of DKA have longer mean latency times on maze testing after DKA recovery compared to rats with streptozotocin-induced diabetes without DKA.[86] This measurable decrease in neurocognitive function raises concern for similar effects in people with DKA, although the underlying mechanism was not examined further via imaging or gross dissection. A recent prospective study of patients ages 6-18 years with and without DKA at diagnosis of T1D demonstrated cerebral white matter changes on MRI that, despite resolution over the first week, resulted in persistent alterations in attention and memory for up to 6 mo later.[88] The greatest risk factors for these changes in cerebral structure were degree of acidosis and younger age at presentation, further highlighting the need for improved DKA prevention.

CONCLUSION

The most common cause of acute deterioration in children with DKA is cerebral edema, the pathogenesis of which remains under active investigation and discussion. Other rare complications of pediatric DKA include acute changes in coagulation, pulmonary function, musculoskeletal and gastrointestinal health as well as long-term cognitive outcomes (Table 1). These findings are rare and require a high index of clinical suspicion, but early recognition and treatment may help avoid permanent deficits. More data related to the presentation, treatment and outcome of these complications in pediatric DKA patients is still needed, therefore, avoidance of DKA in children and adolescents through public and professional awareness is paramount to preventing these acute and chronic complications.

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