In: Pediatric Diabetic Ketoacidosis ISBN: 978-1-63483-220-5
Editors: S. C. Duck and J. R. Hageman

Chapter 6

COMPLICATIONS AND OUTCOMES OF PEDIATRIC DIABETIC KETOACIDOSIS

G. Todd Alonso, MD
University of Colorado, Denver, CO, US
Barbara Davis Center for Childhood Diabetes, Aurora, CO, US

ABSTRACT

Diabetic ketoacidosis (DKA) is a frequent occurrence in diabetes mellitus. Despite advances in care, a small percentage of children suffer complications which can have devastating outcomes. The most common of these complications is cerebral edema. While contributing factors and mechanisms which predispose patients with DKA to cerebral edema are only partially understood, current consensus statements from professional societies such as the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes are able to provide clear guidance based on the best available evidence for optimizing outcomes in pediatric DKA.

INTRODUCTION

Diabetic ketoacidosis (DKA) is a complicated disease process characterized by many coexisting metabolic derangements. Absolute or relative insulin deficiency causes hyperglycemia, a resultant osmotic diuresis,

and subsequent dehydration, hyperosmolarity, and electrolyte imbalances. Simultaneously, fatty acid breakdown leads to metabolic acidosis. Together, these factors put the patient at risk for organ damage which can cause permanent disability or death. Initiating appropriate therapy does not always guarantee an optimal outcome. Complications may arise during the hospital course, necessitating vigilance from the medical team. Many patients with DKA require the intensity and expertise available only in a critical care unit. For these reasons, the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends that children and adolescents who present with DKA be treated in centers with pediatric DKA experience where frequent monitoring of vital signs, neurological status, and laboratory assessments are possible. In cases where geography limits access to such a center, it is recommended that arrangements for telephone or videoconference support from a physician with experience with DKA be established.

A seven year retrospective study of pediatric DKA in the United Kingdom found that children with type 1 diabetes (T1D) have an overall mortality odds ratio (OR) of 2.3 compared to age matched controls [1]. An even higher mortality OR of 9.2 is noted among the 1 to 4 year old age group. Diabetic ketoacidosis was implicated in 82% of all deaths, and cerebral edema was present in at least 62% of all in-hospital deaths. Cerebral edema (CE-DKA) is the most common cause of death in patients with T1D.

Mortality for each episode of DKA ranges from 0.08 to 0.3%, with evidence of improving trends [1–4], likely a result of increased understanding of the inherent risks of DKA and the evolution of evidence based treatment protocols. Because CE-DKA is the major source of morbidity and mortality in pediatric DKA, many of the specific recommendations in DKA treatment algorithms are directed towards minimizing the occurrence and guiding the management of this frightening complication.

CEREBRAL EDEMA

Cerebral Edema – Epidemiology

Multicenter studies indicate that the incidence of clinically evident CE-DKA is 0.6-0.9% [5–7]. One retrospective series of 17 cases noted the timing of the identification of signs of brain swelling to range from as early as 180 minutes to as long as 30 hours after initiating therapy for DKA [8]. Others report evidence of CE-DKA even before intravenous therapy began. Cerebral

edema is far less common in adults [9], although the protective factors that develop in older persons with T1D are not understood. Because CE-DKA is such a rare consideration in adult DKA, facilities with pediatric specific critical care will be the best equipped to care for these patients.

While CE-DKA is only diagnosed in a minority of pediatric patients, evidence of subclinical cerebral pathology has been detected in a majority of pediatric patients with DKA. Cranial computed tomography scans done prior to initiating therapy in seven of nine patients showed smaller lateral and third ventricles compared to the noted sizes in follow up scans seven days later. However, only one patient in that group was diagnosed with CE-DKA [10]. A study using cranial magnetic resonance imaging (MRI) also found ventricular narrowing in 22 of 42 pediatric patients with DKA [11]. Cerebral oximetry evaluation in 19 patients with DKA aged 8 to 18 years revealed that 90% had evidence of cerebral hyperemia as early as the second hour of treatment which persisted beyond 24 hours in at least four [12]. Therefore, subclinical CE-DKA is a common phenomenon, albeit of uncertain significance.

Cerebral Edema – Pretreatment Factors

Multiple pretreatment factors are associated with increased odds of developing CE-DKA. Most indicate that patients with more severe metabolic derangements have higher risk. Lower initial HCO_3 [7] and PCO_2 [5, 11, 13], as well as higher initial serum urea [5, 7, 11, 13, 14] and glucose concentrations [7, 13] suggest that greater degrees of acidosis and dehydration at presentation predispose patients with DKA to develop brain swelling. Retrospective analysis of 34 CE-DKA cases demonstrated that the risk for development of CE-DKA was threefold higher in patients with new onset diabetes compared to those with established diabetes (11.9 vs 3.8 per 1000) [6]. The reasons for this difference are not clear. Younger age is also associated with a greater risk of cerebral edema [5, 15]. Therefore, most experts agree that younger age, new onset diabetes, and more severe initial laboratory assessment increase risk for CE-DKA, and admission to pediatric critical care should be considered [16].

Neuroinflammation appears to be an important event in the development of CE-DKA. Pathologic examination of cerebral tissue from fatal cases of CE-DKA revealed increased expression of proinflammatory mediators and disruption of vascular tight junctions, leading to structural and functional alteration of blood brain barrier integrity [17]. The albumin extravasation

observed in these cases would decrease the relative serum oncotic pressure, and thus potentiate vasogenic edema in the brain. A vasogenic rather than a cytotoxic process is further supported by elevated apparent diffusion coefficients on cerebral MRI [11] and by multiple reports of rapid neurological improvement with the intravenous infusion of mannitol or hypertonic saline [18]. Despite all the known associations in CE-DKA, no unified theory sufficiently explains the complicated etiology that predisposes these patients to brain swelling.

Cerebral Edema – Treatment Factors

Knowing that patients with DKA are dehydrated, thirsty, and tachycardic, the temptation is to aggressively administer intravenous (IV) fluid as though treating hypovolemic shock. However, earlier studies indicated that dramatically greater rates of IV rehydration were associated with increased risk of developing CE-DKA [19]. Patients presenting with DKA have increased osmolarity throughout the body from elevated sodium, glucose, and urea concentrations which developed over hours to days. Therefore, a treatment induced rapid drop in serum osmolarity due to the administration of relatively hypotonic IV fluids was hypothesized to be a major driving force behind CE-DKA. Whereas quickly decreasing serum osmolarity would occur in minutes, the blood brain barrier prevents an equally rapid adjustment, leading to free water influx into the brain tissue.

Although two pediatric DKA studies failed to show an association between CE-DKA and total fluid volume administered [5, 20], larger IV fluid volume in the first four to eight hours of DKA management was associated with an increased CE-DKA risk [20, 21]. Additionally, in a review of 12 CE-DKA cases, patients were more likely to have experienced not only a larger decrease in effective plasma osmolarity early in the course of therapy, but also to have had higher urine output and a more positive fluid balance [21]. Therefore, while the question of optimal IV fluid rate and content is still outstanding, most pediatric DKA protocols restrict initial IV fluid boluses to 10-20 mL/kg, reserve further boluses for signs of shock, and propose limits to ongoing IV hydration to minimize the risk of CE-DKA [16]. When treating a patient with DKA, it is important for the clinician to recall that in addition to dehydration, the acidosis is also a strong stimulator of tachycardia. Only a minimal decrease in heart rate is noted in the first hour of rehydration, regardless the volume of fluid given.

Notwithstanding cautious fluid management, other data suggest the genesis of CE-DKA is very complicated. As discussed above, brain swelling prior to the administration of IV fluids is common. A retrospective analysis of the causes of death in pediatric patients with T1D found that eight of the 24 out-of-hospital deaths in those with probable or definite DKA had brain swelling on postmortem examination. Taken together, 5-19% of pediatric patients with DKA have clinical findings of brain swelling prior to receiving IV fluid therapy [5, 7, 22–24]. Therefore, IV fluid content and rate cannot fully explain the development of CE-DKA.

In 2013 White and Dickson reported a rate of CE-DKA of only 0.5% in 3712 DKA admissions at a single center. No deaths from CE-DKA occurred [3]. Their protocol used IV hydration rates about 30% greater than those outlined in recent consensus statements [16, 25, 26]. The authors suggested that their favorable outcomes may be partly attributable to use of 0.675% NaCl, which provided a higher tonicity to the maintenance fluid and may satisfy an ideal tonicity for DKA resuscitation. Ongoing studies are expected to identify an optimal fluid and electrolyte replacement protocol in DKA.

Insulin administration in the first hour of therapy has been associated with increased odds of developing CE-DKA [20]. Further study found it to be more likely in patients who received an IV insulin bolus early in therapy than in those who did not [21]. Because of these data and the fact that blood glucose drops quickly with the initial IV fluid bolus, experts agree that an IV insulin bolus is unnecessary and perhaps even dangerous in DKA.

Limited data exists regarding an association between bicarbonate administration in DKA and the risk of CE-DKA. A 2011 systematic review found three pediatric nonrandomized studies addressing the question [27] (p20). In a multicenter case-control study involving 61 children with CE-DKA administration of bicarbonate was the only treatment factor associated with a greater risk (relative risk 4.2) of cerebral swelling when compared with matched controls [5]. Two smaller studies found a trend towards a similar association, but the effect was nonsignificant after controlling for covariates [7, 20].

Additionally, bicarbonate use in DKA has been associated with a paradoxical increase in cerebrospinal acidosis that could exacerbate hypokalemia. Among the most severely acidotic patients (initial pH < 6.85), controlled trials have failed to show any clinical benefit from bicarbonate therapy. Published data are quite limited. For all of these reasons, while ISPAD does not proscribe the administration of IV bicarbonate, their consensus statement does include a cautious warning about its use [16].

Whereas one of the traditional therapies for cerebral edema was airway intubation with hyperventilation, current evidence indicates that it could actually be counterproductive in the treatment of DKA. Hyperventilation has the potential to decrease brain swelling via arterial autoregulation. Decreasing pCO_2 leads to cerebral artery constriction and therefore less hydrostatic pressure, allowing free water to travel out of the brain parenchyma. However, in a review of 61 cases of CE-DKA from 10 centers, hyperventilation was associated with poorer neurologic prognosis [14]. The authors speculate that decreased cerebral blood flow contributes to cerebral ischemia, potentially exacerbating evolving brain injury. Thus, intubation and mechanical ventilation should be reserved for impending respiratory failure. A review involving 85% of tertiary care pediatric hospitals in the US found that 17.8% of CE-DKA patients were mechanically ventilated [4]. Respiratory arrest in the setting of CE-DKA carries a very poor prognosis [6].

Cerebral Edema – Diagnosis

Patients may develop symptoms of CE-DKA any time from before presentation to the hospital to as late as 30 hours following initiation of therapy [8]. Clinical findings range from nonspecific changes in mental status such as somnolence or irritability to obvious signs of cerebral herniation (Table 1). A review of 26 cases of severe CE-DKA and 69 episodes of uncomplicated DKA was used to develop a bedside evaluation protocol with a 92% sensitivity and 4% false positive rate [8]. At least one diagnostic criterion was positive in all cases, and included abnormal response to pain, decorticate or decerebrate posturing, cranial nerve palsy (especially III, IV, and VI), and abnormal respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis). Cranial nerve palsies and papilledema are specific neurological signs caused directly by increased intracranial pressure. As pressure inside the cranial vault increases, the sympathetic nervous system is stimulated, resulting in constriction of the body's arterioles and thereby causing hypertension. Increased blood pressure then stimulates baroreceptors in the aortic arch, triggering a parasympathetic response which slows the heart rate. Usually late signs, the development of hypertension and bradycardia during treatment for DKA are grave indicators.

Table 1. Clinical findings in 34 cases of CE-DKA [6]

Reduced level of consciousness	100%
Hypertension and bradycardia	41%
Pupil abnormalities	35%
Decerebrate or decorticate posturing	15%
Respiratory arrest	29%

Early recognition and treatment of CE-DKA is critical. A review of 69 cases found that over half of the 23 in whom therapy for the brain swelling was initiated early survived intact or disabled. Only 3 of the 46 who were treated late or not at all survived [15].

Neuroimaging has an unsatisfactory sensitivity for identification of CE-DKA. Glaser et al., showed that a brain CT could be normal even after the development of the first signs of CE-DKA [8, 28]. Moreover, a CT scan requires the patient to be out of the intensive care unit. Therefore, the physician should rely primarily on clinical diagnosis. Therapy for clinically suspected CE-DKA should not be delayed for cranial imaging. As discussed below, emergent brain CT may be considered in a critically ill patient with encephalopathy or acute focal neurologic deficit for the identification of a lesion which requires emergency neurosurgery (e.g., intracranial hemorrhage) or anticoagulation (e.g., cerebrovascular thrombosis) [16].

Cerebral Edema – Treatment

Because of the known association between IV fluids and CE-DKA, fluid rate should be decreased and the head of the bed elevated 30 degrees as soon as CE-DKA is suspected. Hyperosmolar IV fluids should be available at the bedside and administered without delay. In the past, mannitol, a nonmetabolized sugar alcohol, was the usual agent considered for the treatment of CE-DKA. However, 3% hypertonic saline more recently became an acceptable alternative [29], possibly because of easier storage at the bedside. Though the mechanism is unclear, both agents are believed to improve cerebral blood flow through decreased blood viscosity and reducing the intracellular volume via osmotic effects on the brain neurons [4]. Many observers cite rapid improvement in patients' clinical status upon administration of either agent.

In a review of over 43,000 pediatric DKA cases throughout the United States from 1999 to through 2009, 3.8% of patients were treated with hyperosmolar therapy. Most received mannitol as a sole agent, but 3% sodium chloride infusion increased during that time [4]. The authors called for clinical equipoise regarding the use of one agent over the other because of higher mortality (adjusted odds ratio 2.71) when 3% saline was used alone. This will need to be investigated with a prospective trial.

Cerebral Edema – Outcome

CE-DKA was the identified cause for 50 to 60% of diabetes related deaths in children [1, 15]. The mortality for patients with CE-DKA is now reduced to 21-24% [5–7, 14]. In addition, 57 to 65% of CE-DKA survivors have no long-term neurologic sequelae [5, 6, 14]. Persistent neurologic deficits in CE-DKA survivors include motor deficits, visual impairment, short term memory loss, dysphasia, dysarthria, and learning and emotional problems.

OTHER CONDITIONS COMPLICATING DKA

After CE, a variety of other problems account for the remaining morbidity and mortality in pediatric DKA. Each of these conditions is relatively rare and much less thoroughly studied in DKA than CE, though enough literature exists to aid clinicians' decision-making.

Hypercoagulability/Thrombosis

Reports of cerebral and deep venous thromboses indicate that DKA is a hypercoagulable state. Dehydration, osmolarity, tissue hypoxia, acidosis, and hyperlipidemia are some of the factors which have been proposed to promote thrombosis in these patients. Coagulation assessment in DKA demonstrated transiently increased von Willebrand Factor and decreased levels of protein C and decreased activity of protein S [30] in patients with no underlying clotting abnormalities. Some patients who experience severe thrombotic events during DKA have been found to have underlying hypercoagulable disorders such as sickle trait [3] and protein S deficiency [31]. Acute, focal neurologic deficits, seizures, decerebrate posturing, hemiparesis, or respiratory failure during an

episode of DKA should raise suspicion for cerebral thrombosis, and brain imaging may be appropriate.

A case control study in children who underwent femoral venous catheterization during DKA indicated an increased risk for deep venous thrombosis when compared to other children in shock [32]. The risk was especially high for infants and toddlers. The authors suggest that a thrombosis prophylaxis regimen would be rational in this population.

Potassium Derangements

Abnormal serum potassium levels are very common in DKA. Dehydration leads to avid renal sodium retention through the renin/angiotensin/aldosterone pathway at the expense of a large urinary potassium loss. However, as most of the body's potassium is intracellular, serum potassium measurements do not reflect the state of depletion, and therefore patients may present with hyper-, normo-, or hypo-kalemia. Insulin administration shifts potassium intracellularly, potentially causing a dangerous degree of hypokalemia. In their series, Glaser et al., reported two deaths from hypokalemia and hypocalcemia which led to cardiac arrest [5]. The authors advise that patients have continuous electrocardiographic (ECG) monitoring of lead II if the initial serum potassium level is ≤3 mEq/L or ≥6 mEq/L. ECG abnormalities seen in the setting of abnormal potassium levels are shown below:

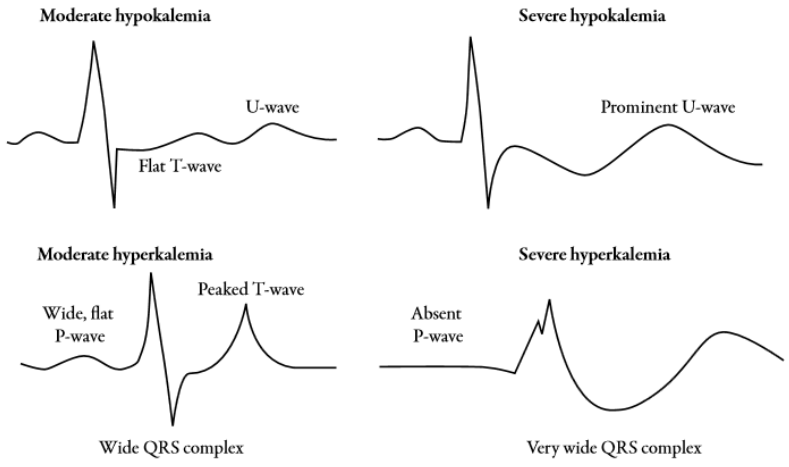

Figure 1. Electrocardiographic patterns for hypo- and hyperkalemia [33].

If hypokalemia causes severe ECG changes, insulin therapy should be withheld until sufficient potassium can be administered, and then insulin can be infused at a slower rate [34].

Hypophosphatemia

The osmotic diuresis of evolving DKA also causes phosphate loss. Insulin therapy drives phosphate intracellularly, potentiating hypophosphatemia. Severe hypophosphatemia is rare, but can lead to metabolic encephalopathy, seizure, impaired myocardial contractility, respiratory failure, dysphagia, ileus, hemolysis, and rhabdomyolysis, and reduced oxygen release from hemoglobin [16]. Overly aggressive IV phosphate replacement can lead to hypocalcemia. Small, prospective studies failed to show benefit of phosphate replacement during DKA therapy [16], but most centers administer some phosphate in their DKA resuscitation fluids.

Cardiac Arrhythmias

A prolonged QTc interval occurs frequently during DKA and correlates with the level of ketosis [35]. Additionally, T wave inversion has also been reported during DKA in the setting of normokalemia, which the authors postulate could be due to tachycardia or hyperventilation leading to poor coronary artery filling [36].

Rhabdomyolysis

Rhabdomyolysis is a relatively common complication in patients presenting with hyperglycemic hyperosmolar state, but far more infrequent in DKA [33]. Myoglobinuria will not necessarily cause darkened urine, and laboratory tests for myoglobinuria lack sensitivity [37]. Therefore, muscular weakness accompanied by low phosphate or potassium levels should raise suspicion for rhabdomyolysis. Renal failure, also very rare in pediatric DKA, is associated with rhabdomyolysis and should prompt consideration of dialysis [33].

Pancreatitis

Acute pancreatitis is diagnosed in about 2% of children with DKA, whereas the incidence is closer to 10% in adults [38]. Elevations in serum amylase and lipase are much more common, present in 40% of pediatric DKA [38]. Most of the amylase is believed to be from salivary origin, and the lipase level is directly associated with the degree of acidosis [33]. Therefore, providers should evaluate a patient for pancreatitis when abdominal pain is greater than expected for the clinical condition or does not abate with standard DKA therapy.

About 40% of children with DKA have elevated triglycerides, but the levels are usually not in the range expected to lead to acute pancreatitis (> 1000 mg/dL) [38]. Plasmapheresis has been used successfully to treat severe hypertriglyceridemia in a child with DKA and pancreatitis [39]. Patients who present with severe triglyceride elevations do not necessarily have familial hypertriglyceridemia [40].

Infections

Patients with DKA may be at increased risk of infection, but sepsis appears to be exceedingly rare in this group. During DKA, neutrophils have impaired chemotaxis and are less able to generate reactive oxygen species [41]. Mucormycosis is a rare, opportunistic infection experienced by a very small number of patients with DKA, but it is associated with a grave prognosis [33]. One series indicated a mortality rate of 40% when there was cerebral involvement [42].

Pulmonary Edema

Acute pulmonary edema and adult respiratory distress syndrome have been reported in children with DKA [43]. Pulmonary CT scans in children with DKA demonstrated interstitial pulmonary edema, even very early in therapy [10]. The mechanisms for these findings are unclear, but could represent pathology similar to cerebral edema.

Neurocognitive Effects

Although overall intellectual abilities in children with T1D are typically normal, there are detectable deficits in memory performance [44, 45]. In the past, most of the concern for neurocognitive deficits in patients with T1D focused on the effects of hypoglycemia [46], but there is now growing evidence that DKA events are associated with disrupted memory function [47, 48].

CONCLUSION

Diabetic ketoacidosis represents a dangerous set of metabolic abnormalities brought about by insulin deficiency leading to hyperglycemia, osmotic diuresis, and acidosis. While there are many potential complications in DKA therapy, cerebral edema is by far the most dangerous. Fortunately, modern DKA therapy results in complete recovery for almost all patients. Key principles for optimal outcomes include judicious fluid and electrolyte replacement, close monitoring of clinical signs and laboratory assessments, and treatment in a facility with the expertise and tools to provide appropriate therapy and manage complications.

REFERENCES

[1] Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990–96. *Arch. Dis. Child*. 1999;81(4):318-323.

[2] Curtis JR, To T, Muirhead S, Cummings E, Daneman D. Recent Trends in Hospitalization for Diabetic Ketoacidosis in Ontario Children. *Diabetes Care*. 2002;25(9):1591-1596. doi:10.2337/diacare.25.9.1591.

[3] White PC, Dickson BA. Low Morbidity and Mortality in Children with Diabetic Ketoacidosis Treated with Isotonic Fluids. *J. Pediatr*. 2013;163(3):761-766. doi:10.1016/j.jpeds.2013.02.005.

[4] DeCourcey DD, Steil GM, Wypij D, Agus MSD. Increasing Use of Hypertonic Saline Over Mannitol in the Treatment of Symptomatic Cerebral Edema in Pediatric Diabetic Ketoacidosis: An 11-Year Retrospective Analysis of Mortality*. *Pediatr Crit. Care Med*. 2013;14(7):694-700. doi:10.1097/PCC.0b013e3182975cab.

[5] Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. *N. Engl. J. Med*. 2001;344(4):264-269.

[6] Edge JA, Hawkins MM, Winter DL, Dunger DB. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch. Dis. Child*. 2001;85(1):16-22.

[7] Lawrence SE, Cummings EA, Gaboury I, Daneman D. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. *J. Pediatr*. 2005;146(5):688-692. doi:10.1016/j.jpeds.2004.12.041.

[8] Muir AB, Quisling RG, Yang MCK, Rosenbloom AL. Cerebral Edema in Childhood Diabetic Ketoacidosis Natural history, radiographic findings, and early identification. *Diabetes Care*. 2004;27(7):1541-1546. doi:10.2337/diacare.27.7.1541.

[9] Azzopardi J, Gatt A, Zammit A, Alberti G. Lack of evidence of cerebral oedema in adults treated for diabetic ketoacidosis with fluids of different tonicity. *Diabetes Res. Clin. Pract*. 2002;57(2):87-92.

[10] Hoffman WH, Steinhart CM, Gammal T el, Steele S, Cuadrado AR, Morse PK. Cranial CT in children and adolescents with diabetic ketoacidosis. *Am. J. Neuroradiol*. 1988;9(4):733-739.

[11] Glaser NS, Wootton-Gorges SL, Buonocore MH, et al. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. *Pediatr Diabetes*. 2006;7(2):75-80. doi:10.1111/j.1399-543X. 2006.00156.x.

[12] Glaser NS, Tancredi DJ, Marcin JP, et al. Cerebral Hyperemia Measured with Near Infrared Spectroscopy during Treatment of Diabetic Ketoacidosis in Children. *J. Pediatr*. 2013;163(4):1111-1116. doi:10.1016/j.jpeds.2013.06.008.

[13] Fiordalisi I, Novotny WE, Holbert D, Finberg L, Harris GD. An 18-yr prospective study of pediatric diabetic ketoacidosis: an approach to minimizing the risk of brain herniation during treatment. *Pediatr Diabetes*. 2007;8(3):142-149. doi:10.1111/j.1399-5448.2007.00253.x.

[14] Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J. Pediatr*. 2002;141(6):793-797. doi:10.1067/mpd.2002.128888.

[15] Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. *Diabetes Care*. 1990;13(1):22-33. doi:10.2337/ diacare. 13.1.22.

[16] Wolfsdorf JI, Allgrove J, Craig ME, et al. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2014;15(S20):154-179. doi:10.1111/pedi.12165.

[17] Hoffman WH, Stamatovic SM, Andjelkovic AV. Inflammatory mediators and blood brain barrier disruption in fatal brain edema of diabetic ketoacidosis. *Brain Res*. 2009;1254:138-148. doi:10.1016/j.brainres.2008.11.100.

[18] Tasker RC, Acerini CL. Cerebral edema in children with diabetic ketoacidosis: vasogenic rather than cellular? *Pediatr Diabetes*. 2014;15(4):261-270. doi:10.1111/pedi.12153.

[19] Duck S, Wyatt D. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. *J. Pediatr*. 1988;113(1):10-14.

[20] Edge JA, Jakes RW, Roy Y, et al. The UK case–control study of cerebral oedema complicating diabetic ketoacidosis in children. *Diabetologia*. 2006;49(9):2002-2009. doi:10.1007/s00125-006-0363-8.

[21] Hoorn EJ, Carlotti APCP, Costa LAA, 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(5):467-473. doi:10.1016/j.jpeds.2006.11.062.

[22] Couch RM, Acott PD, Wong GW. Early Onset Fatal Cerebral Edema In Diabetic Ketoacidosis. *Diabetes Care*. 1991;14(1):78-79. doi:10.2337/diacare.14.1.78b.

[23] Glasgow AM. Devastating Cerebral Edema in Diabetic Ketoacidosis Before Therapy. *Diabetes Care*. 1991;14(1):77-78. doi:10.2337/diacare.14.1.77.

[24] Warncke K, Dressel P, Ziegler A-G, et al. Severe Pretreatment Cerebral Edema in Newly Diagnosed Type 1 Diabetes. *Horm. Res. Paediatr*. 2014. doi:10.1159/000357140.

[25] Dunger DB, Sperling MA, Acerini CL, et al. European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society Consensus Statement on Diabetic Ketoacidosis in Children and Adolescents. *Pediatrics*. 2004;113(2):e133-e140. doi:10.1542/peds.113.2.e133.

[26] Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes*. 2009;10:118-133. doi:10.1111/j.1399-5448.2009.00569.x.

[27] Chua HR, Schneider A, Bellomo R. Bicarbonate in diabetic ketoacidosis - a systematic review. *Ann. Intensive Care*. 2011;1:23. doi:10.1186/2110-5820-1-23.

[28] Glaser NS, Wootton-Gorges SL, Buonocore MH, et al. Subclinical Cerebral Edema in Children With Diabetic Ketoacidosis Randomized to 2 Different Rehydration Protocols. *Pediatrics*. 2013;131(1):e73-e80. doi:10.1542/peds.2012-1049.

[29] Curtis JR, Bohn D, Daneman D. Use of hypertonic saline in the treatment of cerebral edema in diabetic ketoacidosis (DKA). *Pediatr Diabetes*. 2001;2(4):191.

[30] Carl G, Hoffman W, Passmore G, et al. Diabetic Ketoacidosis Promotes a Prothrombotic State. *Endocr. Res*. 2003;29(1):73.

[31] Sdogou T, Kossiva L, Kakleas K, et al. Deep Vein Thrombosis and Pulmonary Embolism in a Child with Diabetic Ketoacidosis and Protein S Deficiency: A Case Report. *Horm Res. Paediatr*. 2013;79(2):114-118. doi:10.1159/000343813.

[32] Gutierrez JA, Bagatell R, Samson MP, Theodorou AA, Berg RA. Femoral central venous catheter-associated deep venous thrombosis in children with diabetic ketoacidosis. *Crit. Care Med*. 2003;31(1):80-83.

[33] Rosenbloom AL. The management of diabetic ketoacidosis in children. *Diabetes Ther*. 2010;1(2):103-120. doi:10.1007/s13300-010-0008-2.

[34] Davis SM, Maddux AB, Alonso GT, Okada CR, Mourani PM, Maahs DM. Profound hypokalemia associated with severe diabetic ketoacidosis. *Pediatr Diabetes*. 2014:n/a - n/a. doi:10.1111/pedi.12246.

[35] Kuppermann N, Park J, Glatter K, Marcin JP, Glaser NS. Prolonged QT interval corrected for heart rate during diabetic ketoacidosis in children. *Arch. Pediatr Adolesc. Med*. 2008;162(6):544-549.

[36] Kale T, Agrawal H, Pandit R, Naheed Z. T-Wave Inversion in Diabetic Ketoacidosis with Normokalemia in an Adolescent. *Pediatr Cardiol*. 2013;34(6):1508-1510. doi:10.1007/s00246-012-0411-8.

[37] Kutlu AO, Kara C, Cetinkaya S. Rhabdomyolysis without detectable myoglobulinuria due to severe hypophosphatemia in diabetic ketoacidosis. *Pediatr Emerg. Care*. 2011;27(6):537-538.

[38] Haddad NG, Croffie JM, Eugster EA. Pancreatic enzyme elevations in children with diabetic ketoacidosis. *J. Pediatr*. 2004;145(1):122-124. doi:10.1016/j.jpeds.2004.03.050.

[39] Lutfi R, Huang J, Wong HR. Plasmapheresis to Treat Hypertriglyceridemia in a Child With Diabetic Ketoacidosis and Pancreatitis. *PEDIATRICS*. 2012;129(1):e195-e198. doi:10.1542/peds.2011-0217.

[40] Wolfgram PM, MacDonald MJ. Severe Hypertriglyceridemia Causing Acute Pancreatitis in a Child with New Onset Type I Diabetes Mellitus

Presenting in Ketoacidosis. *J. Pediatr Intensive Care*. 2013;2(2):77-80. doi:10.3233/PIC-13053.

[41] Kumar MM, Poovazhagi V, Anbalagan S, Devasena N. Rhino-orbito-cerebral mucormycosis in a child with diabetic ketoacidosis. *Indian J. Crit. Care Med*. 2014;18(5):334-335. doi:10.4103/0972-5229.132512.

[42] Nithyanadam, Ms J, Rr B, Rk T, Ma C, O D. Rhino-Orbito-Cerebral Mucormycosis. A Retrospective Analysis of Clinical Features and Treatment Outcomes. *Indian J. Ophthalmol*. 2003;51(3):231.

[43] Holsclaw DS, Torcato B. Acute pulmonary edema in juvenile diabetic ketoacidosis. *Pediatr Pulmonol*. 1997;24(6):438-443. doi:10.1002/(SICI)1099-0496(199712)24:6<438::AID-PPUL9>3.0.CO;2-C.

[44] Hershey T, Perantie DC, Warren SL, Zimmerman EC, Sadler M, White NH. Frequency and Timing of Severe Hypoglycemia Affects Spatial Memory in Children With Type 1 Diabetes. *Diabetes Care*. 2005;28 (10):2372-2377. doi:10.2337/diacare.28.10.2372.

[45] Perantie DC, Lim A, Wu J, et al. Effects of prior hypoglycemia and hyperglycemia on cognition in children with type 1 diabetes mellitus. *Pediatr Diabetes*. 2008;9(2):87-95. doi:10.1111/j.1399-5448.2007.00274.x.

[46] Hershey T, Lillie R, Sadler M, White NH. A prospective study of severe hypoglycemia and long-term spatial memory in children with type 1 diabetes. *Pediatr Diabetes.* 2004;5(2):63-71. doi:10.1111/j.1399-543X.2004.00045.x.

[47] Ghetti S, Lee JK, Sims CE, DeMaster DM, Glaser NS. Diabetic Ketoacidosis and Memory Dysfunction in Children with Type 1 Diabetes. *J. Pediatr*. 2010;156(1):109-114. doi:10.1016/ j.jpeds. 2009.07.054.

[48] Cameron FJ, Scratch SE, Nadebaum C, et al. Neurological Consequences of Diabetic Ketoacidosis at Initial Presentation of Type 1 Diabetes in a Prospective Cohort Study of Children. *Diabetes Care*. 2014;37(6):1554-1562. doi:10.2337/dc13-1904.