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Hyperosmolar Diabetic Ketoacidosis in Two Adolescents with New Onset Type 2 Diabetes Mellitus

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Abstract

We present the unique cases of two adolescent patients who presented to a pediatric tertiary care facility in the Midwest United States with newly diagnosed type 2 diabetes mellitus, complicated by the combination of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Each case required intensive therapy with treatment consisting of replacement of fluids over a prolonged period of =>72 hours and careful monitoring of electrolyte response. Complications included acute renal failure, superficial thrombosis, and rhabdomyolysis. The two cases made a complete recovery without neurological sequelae. Both cases highlight the complexity of managing patients with a mixed DKA-HHS presentation and associated morbidities. Implementation of screening guidelines for type 2 diabetes mellitus is vital to prevent such serious complications.

Keywords: Hyperosmolar ; Diabetic; Ketoacidosis

Introduction

A 12 -year-old African American male presented with severe dehydration and altered mental status, in the setting of recent acute viral pharyngitis and increase fluid intake. Patient was obese and found to have acanthosis and mild hepatomegaly by ultrasound scan. He was clinically diagnosed with type 2 diabetes mellitus, which was later confirmed by negative GAD-65, insulin and islet cell antibodies. At presentation, a head computed tomography (CT scan) showed no intracranial abnormalities or cerebral edema. He had marked hyperglycemia (serum glucose 1808 mg/dL), acute kidney injury (serum creatinine 1.91 mg/dL), in addition to hypernatremia (corrected Na 164.3 mmol/L, measured Na 137 mmol/L), hyperosmolarity (serum Osmolarity 409 mOsm/kg), and acidosis (pH 6.98), fitting diagnostic criteria for DKA as well as HHS. (Table 1). He was emergently treated with fluid resuscitation 10 mL/kg 0.9% saline, followed by dextrose 5 % normal saline at 1.5 times maintenance. He was also placed on insulin drip at rate 0.1U/kg/hr and on heparin Subcutaneous (SC) for deep venous thrombosis prophylaxis. Subsequently, dextrose concentration was titrated to keep glucose goal at 150-250 mg/dL. Due to persistent worsening tachycardia with relatively stable blood pressure readings, fluid rate was increased gradually to 2.5 maintenance and sodium content of fluid lowered gradually to 0.37% saline. After resolution of DKA and improvement in hydration, hyperosmolality, and hypernatremia status, IV fluids were switched to a maintenance rate, and the insulin drip rate was titrated to maintain glucoses between 150-250 mg/dL. Following, he was started on subcutaneous (SC) insulin at 0.7 U/kg/day and allowed to eat, but was maintained on half-normal saline at maintenance [1].

	Case 1	Case 2	Normal range
Age, years	12	12	
Weight, Kg	88.9	100	
BMI, kg/m2	30.37	39.18	
Admit BG, mg/dL	1808	981	(60-99)
Bicarbonate, mmol/L	5	9	(18-27)
Calculated Anion gap ,mmol/L	30	35	(10-30)
PH	6.98	7.1	(7.38-7.42)
Measured Osmolality ,mOsm/kg	409	372	(280-300)
Sodium, mmol/L	137	134	(136-145)

Corrected Sodium, mmol/L	164.3	148	(136-145)
Potassium, mmol/L	5.7	4.8	(3.5-5.3)
BUN, mg/dL	35	16	(6 -23)
Creatinine, mg/dL	1.91	1.37	(0.2-0.5)
B-hydroxybutyrate , mmol/L	N/A	11.6	(0.02-0.27)
Insulin ,uIU/mL	1	5	(3-19)
Altered mental status	Yes	Yes	
Length of stay, days	14	6	

Table 1: Clinical characteristic and Laboratory values at presentation.

Unfortunately, on the same night, he developed a fever of 39.3 C, with rapid deterioration, and developed septic shock. He was treated with fluid resuscitation and intravenous broad-spectrum antibiotics, and required inotropes for a total of 20 hours. Blood culture reported Enterobacter Cloacae. In addition, he developed a superficial right cephalic vein thrombus. After improvement in clinical status, he was switched back to SC insulin and was transferred to the general pediatrics floor to continue his IV antibiotic course. He was discharged on metformin and SC insulin; total daily dose (TDD) 0.7 U/kg/day [2].

Materials and methods

A 12-year male with a past medical history of epilepsy and asthma presented to the ED with symptoms of fatigue and altered mental status. Patient was obese and found to have acanthosis nigricans, and elevated liver enzymes. He was clinically diagnosed with type 2 diabetes mellitus, which was later confirmed with negative GAD-65, insulin and islet cell antibodies. At presentation, he was hemodynamically stable. A head CT scan was negative for intracranial abnormalities or cerebral edema. He was noted to have hyperglycemia (serum glucose 981 mg/dl), acute kidney injury (serum creatinine 1.37 mg/dL) hypernatremia (corrected Na 148 mmol/L, measured 134 mmol/L), hyperosmolarity (serum Osmolarity 372 mOsm/kg), and acidosis (pH 7.1), consistent with both DKA and HHS (Table 1). Fluid resuscitation with 10 ml/kg 0.9% saline was given, followed by dextrose 5% normal saline at two times maintenance; the dextrose concentration was titrated to keep glucose between 150-250 mg/dL. Insulin drip was started at 0.05 u/kg/hour. After 8.5 hours, sodium content in fluid was decreased to 115 mEq/L (¾ NS) to gradually decrease serum Na and serum osmolality [3].

During the first 12 hours after presentation, his course was complicated by worsening encephalopathy with severe agitation that required IV sedation and physical restraints. Metabolic encephalopathy slowly improved over the following 12 hours. After neurologic status returned to baseline and ketoacidosis had resolved, he was started on SC insulin (0.8 U/kg/day) and was allowed to eat, but was maintained on normal saline IVF at 1.5 maintenance. He was transferred to the pediatric floor [4].

Additionally, the patient was noted to have an elevated creatinine kinase (CK) up to 7000 U/L with hypophosphatemia and hypokalemia. Creatinine kinase trended down with adequate hydration, and he required 4 more days of hydration after starting SC insulin. He required oral potassium and phosphate supplements, and his electrolytes normalized before discharge. He was discharged on metformin 500 mg daily and SC insulin (TDD 1.4 U/kg/day) [5]. Recent epidemiological studies demonstrate that the worldwide incidence of type 2 diabetes is increasing in adolescent age groups. The characteristics and presentation of type 2 diabetes can vary from asymptomatic hyperglycemia, to ketoacidosis in up to 25% of youth, or hyperglycemic hyperosmolar state in up to 2% (1, 2, 3).

DKA and HHS remain the most serious and life-threatening hyperglycemic emergencies in patients with diabetes. The mortality rate of HHS in children is high. Rosenbloom (5) reported that 32 of 97 published cases (32.9%) did not survive, with multiple organ failure being the most common cause of death. Both DKA and HHS can occur in patients with type 1 and type 2 diabetes. HHS typically occurs in older patients with type 2 diabetes with an intercurrent illness; however, recent studies showed an increase of HHS prevalence in children and adolescents. In many patients, features of the two disorders with ketoacidosis and hyperosmolality may also co-exist (5, 6). Agrawal S et al (2018) found that in a pediatric population, a mixed DKA/HHS presentation occurred in 13.8% of characterized hyperglycemic emergencies (7).

Results and Discussion

In cases of mixed HHS and DKA, initial fluid therapy is directed toward expansion of the intravascular and extravascular volume and restoration of renal perfusion (5). Both the American Diabetes Association (ADA) and International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend that the 1st hour of fluids should be isotonic saline (0.9% NaCl). Pediatric specific ADA guidelines from 2004 recommend a bolus at the rate of 10–20 ml/kg/hr versus 20 ml/kg/hr in ISPAD guidelines, and to repeat the bolus until perfusion established. In severe dehydration and hypovolemic shock, ADA guidelines recommend to administer 0.9% NS at the rate of 1 L/hr and/or plasma expander (8, 9).

Subsequent fluid therapy varies between both guidelines. In a typical case of DKA, ISPAD guidelines support a fluid deficit of about 7-10% of the total body weight, and state that total fluid and electrolyte requirements are higher in cases of mixed HHS and DKA, compared to a typical case of DKA. ISPAD guidelines also recommend maintenance fluids (0.45-0.75% saline) plus deficit replacement over 24-48 hr, and replacement of urinary losses with 0.45% saline. However, when there is concern of hypovolemia,

normal saline may be used for urine replacement. In contrast, the ADA guidelines recommend 0.45– 0.9% saline according to serum osmolality, infused at a rate of 1.5 times maintenance requirements over a 48-hour timeframe (8, 9). Both guidelines agree that isotonic fluids should be re-started if at any point there is hemodynamic instability. A rapid rate of decline in serum sodium should be avoided; 0.5 mmol/L/h has been recommended for hypernatremic dehydration. Frequent sodium concentration measurements and fluid adjustments are mandatory to avoid a rapid sodium decline.

Insulin treatment is necessary to resolve ketosis in these patients and continuous insulin infusion should be started after the initial fluid bolus(es). Insulin drip adjustment is recommended to achieve a decline in serum glucose between 50-100 mg/dl per hr. However, re-assessment of fluid and renal function should be carried out before any adjustment. ISPAD guidelines recommend IV insulin of 0.05-0.1 U/kg/hr depending on degree of acidosis. ADA guidelines recommend IV insulin dose at 0.1 U/kg/hr. It should be emphasized that a drop in glucose of over 100 mg/dL/hour may precipitate shock, so close monitoring of the glucose is essential. Often, the glucose will be above the upper limit of detection on a bedside blood glucose meter or even a blood gas, making adjustment of fluids and the insulin drip much more challenging. Close communication with the laboratory to have rapid turn-around of the serum glucose measurement is key to proper management.

Here, we report two patients who presented with a mixed DKA/HHS picture. Impaired cognition was seen in both of them with no evidence of cerebral edema. We believe that the acute encephalopathy was due to the hyperosmolar state. In both patients, mental status improved after hyperosmolarity was corrected. The incidence of clinically overt cerebral edema is 0.5% to 0.9%, and the mortality rate is 21%-24%. Cerebral edema is less common in pediatric HHS cases due to less hypocapnic cerebral vasoconstriction (5). The risk of cerebral edema is higher in mixed DKA/HHS cases than in those with a classical presentation of HHS. Therefore, early vigilant monitoring for fluid replacement and mental status is essential to prevent cerebral edema. However, fluid replacement should never be withheld for fear of cerebral edema, and its importance in preventing complications cannot be emphasized enough (8).

We encountered rhabdomyolysis in ; it is one of the complications that is well documented in both DKA and HHS, but it is more common in HHS. Our patient progressed to rhabdomyolysis shortly after admission, he had depleted intracellular phosphate stores, and extreme hyperosmolar status, acidosis and hyperglycemia; all are known risk factors to develop rhabdomyolysis (10). Hence, ISPAD guidelines recommend monitoring serum CK values in children with HHS every 2-3 hours, as rhabdomyolysis can worsen acute renal failure and precipitate electrolyte abnormalities, cardiac arrhythmias, and even muscle compartment syndrome (8). The severity of dehydration may have been underestimated due to his obesity and serum hypertonicity. Therefore, early and aggressive fluid resuscitation and intensive monitoring are mandatory to prevent this complication.

The other complication we encountered in case #1 was superficial thrombosis at site of peripheral line at day 6 of admission. On admission, Enoxaparin sodium was not a viable option due to impaired renal function. Therefore, he was started on SC heparin for DVT prophylaxis. Unfortunately, he developed thrombocytopenia at day 5 of admission, so SC heparin was discontinued. It is known that diabetes is a hypercoagulable state, explained by endothelial abnormalities and smooth muscle dysfunction favoring coagulation cascade activation (11). In addition, severe dehydration and hypertonicity can activate the coagulation pathway and cause venous stasis. Deep vein thrombosis has been reported in critically ill children who required central venous catheter placement (11, 12). Thromboembolic complications occur commonly in HHS and heparin treatment should be reserved for children who require central venous catheters and are immobile for >24 hours (13).

Conclusion

In conclusion, appropriate screening for children at risk for type 2 diabetes is essential to prevent the life-threatening complications of DKA and HHS. ISPAD recommends to screen children who are > 10 years of age, or younger if pubertal, and who have risk factors for diabetes, including obesity (BMI> 95th for age and sex), member of a high-risk ethnic group, and/or family history of type 2 diabetes (1), among others. Both of our patients are severely obese (BMI>99th for age and sex), and African-American, but never had type 2 diabetes screening.

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