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Case Report

Severe hypernatremia in soft drink ketoacidosis and hyperglycemic hyperosmolar state at the onset of type 2 diabetes mellitus: a case series of three adolescents

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Highlights

- The incidence of mixed diabetic ketoacidosis and hyperglycemic hyperosmolar state in children is increasing.
- Severe hypernatremia in mixed diabetic ketoacidosis and hyperglycemic hyperosmolar state has rarely been reported in the literature.
- Excessive consumption of carbohydrate-rich beverages can exacerbate symptoms, resulting in a more severe presentation at the onset of diabetes.

Abstract. Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are diabetic emergencies. Some patients with a hyperglycemic crisis can present with an overlap of DKA and HHS. The coexistence of DKA and HHS is associated with higher mortality than in isolated DKA and HHS. In addition, electrolyte derangements caused by global electrolyte imbalance are associated with potentially life-threatening complications. Here, we describe three cases of mixed DKA and HHS with severe hypernatremia at the onset of type 2 diabetes mellitus. All patients had extreme hyperglycemia and hyperosmolarity with acidosis at the onset of diabetes mellitus. They consumed 2 to 3 L/d of high-carbohydrate drinks prior to admission to relieve thirst. They showed severe hypernatremia with renal impairment. Two patients recovered completely without any complications, while one died. Severe hypernatremia with mixed DKA and HHS is rare. However, it may be associated with excess carbohydrate beverage consumption. Reduced physical activity during the COVID19 pandemic and unhealthy eating behaviors worsened the initial presentation of diabetes mellitus. We highlight the impact of lifestyle factors on mixed DKA and HHS.

Key words: diabetes mellitus, diabetic ketoacidosis, hyperglycemic hyperosmolar state, diet

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Introduction

Diabetes mellitus is one of the most common endocrine disorders in children and is rarely fatal at presentation (1). However, there are two serious acute metabolic complications of diabetes which are diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). DKA and HHS may be considered as related disorders that are part of a disease continuum. In clinical practice, these two conditions overlap significantly (2). Given the limited data available in the literature, some studies have reported that a mixed presentation of DKA and HHS is not rare in patients hospitalized with acute hyperglycemic crisis. It is seen in up to 14% of children (3) and 29% of youths with diabetes (4). The combination of DKA and HHS is associated with higher mortality than in isolated DKA and HHS (2).

As sodium levels in DKA and HHS are usually low, normal, or slightly elevated, these conditions are induced by dilution of extracellular fluid and/or dehydration due to osmotic diuresis (5). Severe hypernatremia with mixed DKA and HHS is rare, and hypernatremia with hyperglycemia indicates profound dehydration. To date, only a few cases of pediatric mixed DKA and HHS with severe hypernatremia have been reported (6–8). According to a report by McDonnell *et al.*, five out of 100 children with DKA followed up for over two years, presented with severe hyperosmolarity and hypernatremia (8). We identified three patients with mixed DKA and HHS who had severe hypernatremia during the COVID19 pandemic of 2021. Each patient was obese and consumed large amounts of high-carbohydrate beverages prior to admission. We suspect that high-carbohydrate fluid intake in large volumes to relieve polydipsia may precipitate a more severe presentation of diabetes mellitus (8). This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the institutional review board (IRB no. CNUH-EXP-2021-050).

Case Report

The first case was a 15-yr-old male who presented with a 1-wk history of polyuria, polydipsia, and weight loss of 7 kg in the previous 1–2 wk. Diabetes was suspected during health screening in his school one month prior to admission. However, his blood glucose level was not elevated at the time. Two days before admission, he suddenly developed a high fever and muscle pain with generalized weakness that continued to worsen. A blood glucose level of 1288 mg/dL and venous blood pH of 7.29 were detected, and the patient was referred to our department for emergency hospitalization. The initial vital signs were as follows: blood pressure, 100/50 mmHg; pulse rate, 124 beats per min; respiratory rate, 20 breaths per min; and temperature, 38.1°C. On physical examination, he was alert and had central obesity with purple striae over the abdomen. His height was 170 cm (25 to 50th percentile) and weight was 91 kg (> 99th percentile). His body mass index was 31.5 kg/m^2 (> 99th centile) and waist circumference was 109 cm. In the week preceding the diagnosis, he consumed approximately 2–3 L of full-fat milk and 2 L of juice or coke per day instead of water. A diagnosis of mixed DKA and HHS was made based on the levels shown in **Table 1**. The actual sodium level was 146 mEq/L, but his adjusted sodium level was 160 mEq/L (**Fig. 1**). The patient received 3 L of isotonic fluid (NaCl 0.9%) during the first three hours. Since the corrected sodium levels were already high, intravenous fluid was switched to 0.45% NaCl along with continuous insulin infusion (0.05 unit/kg/h). The patient received approximately 8 L of fluid within 24 hours. Serum sodium levels were elevated to 166 mEq/L during fluid therapy, and we changed the sodium concentration with an infusion of 0.3% NaCl in 3.3% dextrose water. The patient's sodium levels returned to the normal range after three days of admission. During hospitalization, lipase levels peaked to 1,421 U/L, while creatine kinase levels reached a peak of 3,457 mg/dL. Abdominal computed tomography revealed swelling of the pancreas with peripancreatic fluid collection (white arrows) and no dilatations or stones in the common bile duct (**Fig. 2**). The insulin infusion rate was increased stepwise up to 0.1 unit/kg/h, while administration of large volumes of hydrating fluids was continued. Acute pancreatitis and rhabdomyolysis slowly improved (**Fig. 1**). On day eight of admission, continuous insulin infusion was transitioned to subcutaneous insulin injection. The patient recovered well and was discharged uneventfully on day 15. He received individualized dietary advice, and his blood glucose levels remained in good control with diet therapy and medication.

The second case was an 11-yr-old male who presented with a 3-d history of nausea, vomiting, and weight loss of 7 kg over a week. A few weeks before admission, he had a history of polyuria and polydipsia. His typical fluid intake prior to admission consisted of 1–2 L of high fat milk and 1 L of carbonated drinks per day. His height was 170 cm (> 99th percentile) and his weight was 99 kg (> 99th percentile). His body mass index was 34.1 kg/m^2 (> 99th percentile). His blood pressure was 120/70 mmHg, heart rate was 143 bpm, respiratory rate was 20 breaths/min, and temperature was 36.5°C. His blood glucose level on presentation was 994 mg/dL, and serum osmolality was 391 mmol/kg. His venous blood gas analysis had a pH of 7.06 and HCO_3^- 7.3 mmol/L. A diagnosis of mixed DKA and HHS was made (**Table 1**). The actual sodium level was 148 mmol/L, with an adjusted sodium level of 162 mmol/L (**Fig. 1**). After initial fluid resuscitation with normal saline, he was administered rehydration therapy (half normal saline) and continuous insulin infusion (0.05 unit/kg/h). His hypernatremia worsened during fluid therapy (peaked at 159 mEq/L with a corrected sodium level of 165 mEq/L). However, his sodium level returned to the normal range after four days of admission. The patient completely recovered without any neurological deficits. After an 11-d hospital stay, the patient was

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Table 1. Clinical and biochemical features at admission

	Case 1	Case 2	Case 3
Gender	M	M	M
Age (yr)	15	11	17
Current body weight (kg)	91	99	98
Body weight loss (kg)	7	7	About 20 kg or more
BMI (kg/m^2)	31.5	34.3	not evaluated
BUN (mg/dL)	58.8	39.2	46.5
Creatinine (mg/dL)	2.0	1.4	3.0
Sodium (mEq/L)	146	148	155
Adjusted sodium (mEq/L)	160	162	169
Potassium (mEq/L)	5.4	6.1	4.5
Serum osmolarity (mOsm/kg)	405	381	419
Glucose (mg/dL)	935	994	1015
Anion gap (mEq/L)	22.5	33.7	31.3
Amylase (U/L)	321	113	73
Lipase (U/L)	1421	274	274
Total cholesterol (mg/dL)	319	204	not evaluated
Triglycerides (mg/dL)	1251	232	not evaluated
HDL-cholesterol (mg/dL)	24	40	not evaluated
LDL-cholesterol (mg/dL)	138	131	not evaluated
pH	7.191	7.06	7.28
HCO_3^-*	15.5	7.3	13.7
Autoantibodies*	Negative	Negative	Negative
Fasting insulin (uU/ml)	35.5	11.7	0.8
Fasting c-peptide (ng/ml)	0.7	3.7	0.1
Hb-A1c (%)	9.9	10.7	14.0
Glycated albumin	1.0	1.6	not evaluated
Ketones (urine)	+2	+2	+3
FeNa (%)	0.2	0.8	not evaluated

*Autoantibodies include insulin antibody, glutamic acid decarboxylase antibody, and islet cell antibody. BMI, body mass index; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HCO_3^-, bicarbonate; Hb-A1c, glycated hemoglobin.

discharged after receiving diabetic dietary education.

The third case was a 17-yr-old male who was unarousable in bed after a 2-wk history of polyuria and polydipsia. He had consumed excessive amounts of high-fat milk and carbonated drinks to relieve thirst prior to admission. On arrival at the first hospital, he was drowsy, tachycardic, and hypotensive with a blood pressure of 80/60 mmHg. His blood glucose level on presentation was 1624 mg/dL, and the following venous blood gas values were observed: pH, 7.17; HCO_3^- level, 7.9 mmol/L. The patient visited our department after fluid resuscitation with normal saline (2.5 L) and continuous insulin infusion. His parents said that his recent weight was 120 kg; however, the patient's weight was 98 kg on arrival. He was drowsy and responsive to pain but responded poorly to verbal stimuli. A diagnosis of mixed DKA and HHS was made (**Table 1**). His actual sodium level was 155 mmol/L with an adjusted sodium level of 170 mmol/L (**Fig. 1**). After initial fluid rehydration with normal saline, the rehydration fluid was switched to hypotonic fluid (half-saline). Although his blood pressure was 100/60 mmHg upon admission, it suddenly dropped to 49/40 mmHg. His tachycardia persisted at 150–170/min with a sustained fever. Echocardiography showed a decreased left ventricular filling volume and normal left ventricular function. Hypovolemic shock was suspected, and the patient received additional isotonic fluid to relieve his severe hypovolemia. Despite massive inotropic and vasopressor support (dopamine, dobutamine, epinephrine, and norepinephrine), he required large volumes of fluid replacement to correct his hypotension. His hypernatremia worsened and peaked at 174 mEq/L, with a corrected sodium level of 185 mEq/L. The patient died 15 hours after admission because of cardiac arrest that was refractory to cardiopulmonary resuscitation.

Discussion

Often, DKA and HHS are discussed as separate entities. It was thought that DKA and HHS specifically occur in patients with type 1 and type 2 diabetes mellitus, respectively. However, a mixed presentation of DKA and HHS is not rare in patients hospitalized with acute hyperglycemic crisis. It has been reported in up to 29% of youths with diabetes, according to a recent study (4). Based on the diagnostic criteria for mixed DKA and HHS, such as pH ≤ 7.30, HCO_3^- level ≤ 15 mmol/L, and serum osmolarity ≥ 330 mOsm/L (7), our patients could also be diagnosed with mixed DKA and HHS. Conversely, our cases were different from other mixed DKA and HHS cases since marked hypernatremic hyperosmolarity was present.

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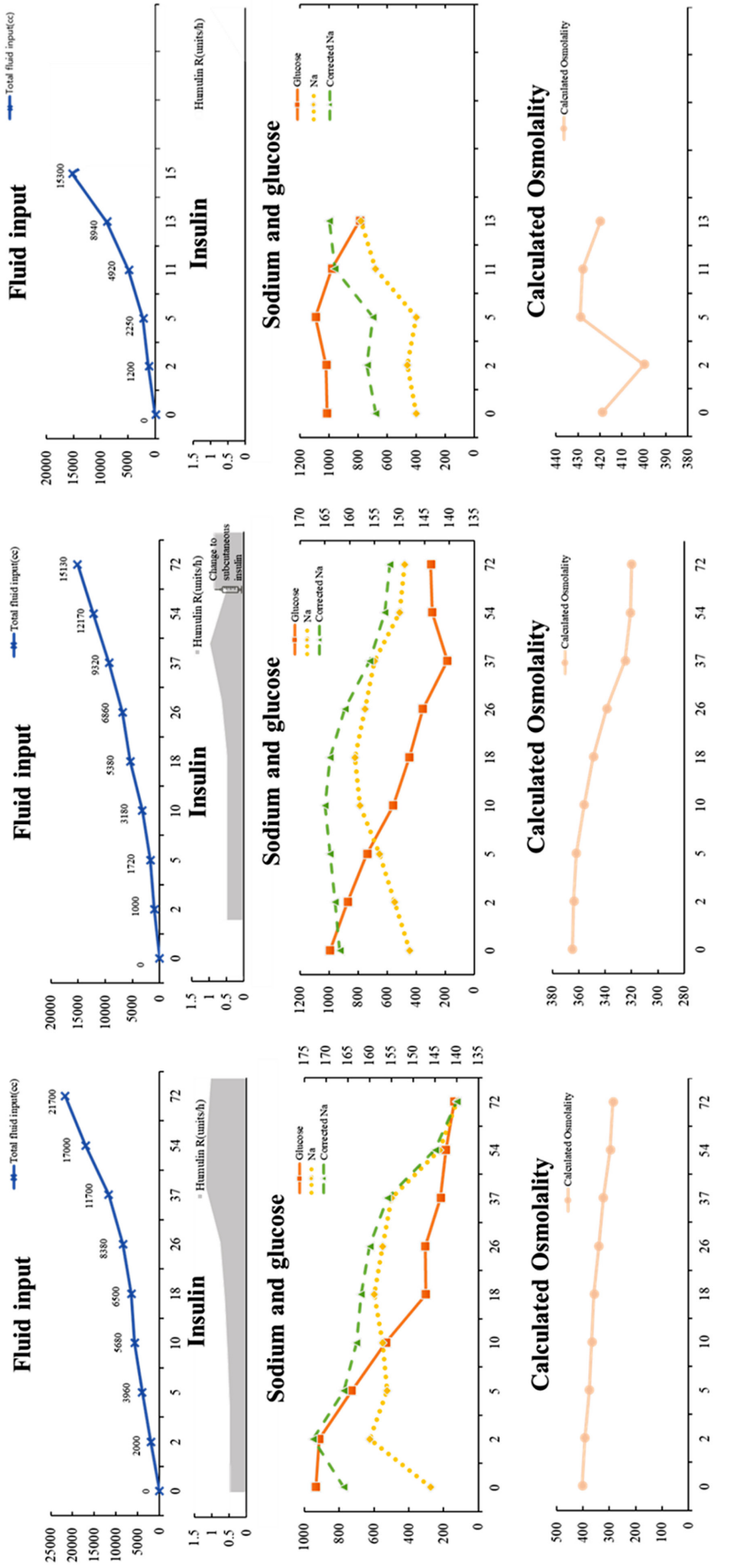

Fig. 1. Therapies and changes of serum glucose level (orange-line), sodium concentration (yellow-line and green-line) and calculated osmolality (blue-line) during the first 3 days of treatment. A. Case 1, B. Case 2, C. Case 3.

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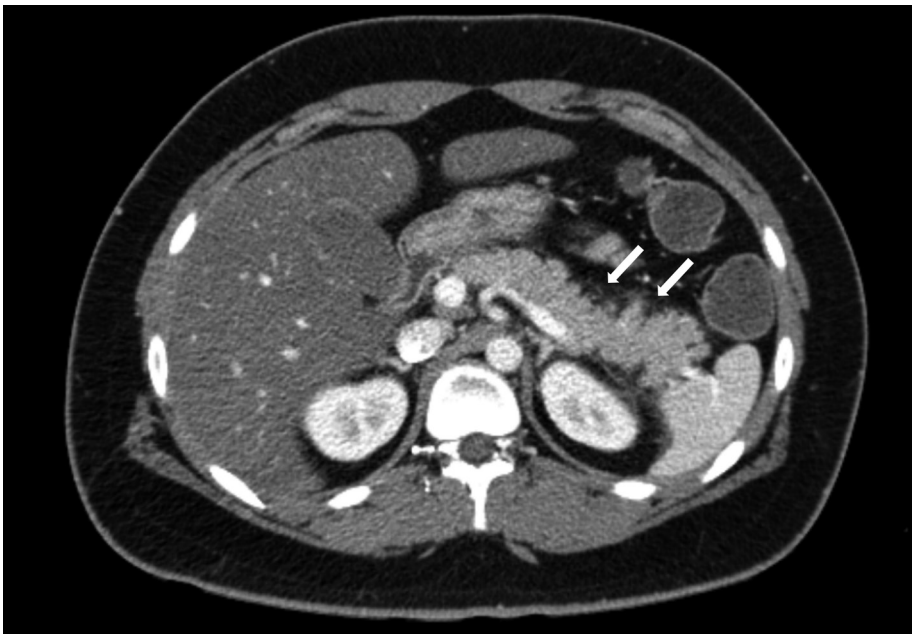

Fig. 2. Transverse section of the abdominal computed tomography scan showing diffuse enlargement of the pancreas with ill-defined borders and surrounding peripancreatic fluid collection (white arrows).

Since the first report of pediatric HHS in 1966 (9), the incidence of HHS in children and adolescents has increased significantly (10). The hospitalization rate of children with HHS increased by 52.4% between 1997 and 2009, with a reported yearly increase of 4.4% (11). This is attributed to an increase in the prevalence of pediatric type 2 diabetes (T2D). However, the overall proportion of patients with mixed DKA and HHS remains unknown. Given the limited data regarding the frequency, clinical characteristics, and prognosis of patients presenting with mixed HHS and DKA, Agrawal *et al*. noted that the majority of cases of mixed HHS and DKA were misdiagnosed or incorrectly diagnosed, leading to 3.1 times higher odds of complications compared to those correctly diagnosed (3). Some small studies have also reported that patients with mixed HHS and DKA have higher mortality rates than those with isolated DKA or HHS (4). In addition, in hypernatremia, serum sodium levels greater than 160 mEq/L is a marker of severity in HHS (12). Both dehydration and electrolyte loss are profound in HHS. Moreover, HHS usually leads to hyponatremia or eunatremia. An increase in serum sodium levels in the presence of hyperglycemia indicates severe dehydration. In this study, each patient consumed large daily amounts of carbohydrate beverages (e.g., coke and juice) to relieve thirst. Increased consumption of carbohydrate-rich beverages exacerbated glucose-induced osmotic diuresis and resulted in worsening severe intravascular dehydration. Hypernatremia at the onset of diabetes may result from the most severe HHS caused by this malicious cycle (5, 8). To restore the water deficit, a large amount of fluid is needed, and isotonic saline is recommended as the first choice in emergency conditions. After achieving hemodynamic stability, it is important to switch to other solutions according to the corrected plasma sodium level with the aim of avoiding treatment-related dysnatremia. Because many variables affect the plasma sodium level variation over time, electrolytes should be checked at least every 2–4 h in order to guide therapy (13). There have been a few reports of mixed DKA and HHS with hypernatremia. It usually occurs in older patients with renal impairment (1). Most pediatric cases have a common history of excessive consumption of carbonated, carbohydrate-rich fluids with sodium content (6–8). In our cases, all the patients had consumed a large amount of juice and coke daily to alleviate their thirst. These drinks usually contain large amounts of sugar and sodium content. Intake of copious quantities of carbonated sugar-enriched drinks can induce severe hyperglycemia and severe dehydration. Therefore, clinicians should identify lifestyle factors in patients with T2D who present with severe symptoms.

Furthermore, intake of sugar-sweetened beverages was significantly associated with greater weight gain and a greater risk of obesity over time. Obesity and hyperosmolality can make the clinical assessment of dehydration unreliable. Thus, early detection of this complication is difficult. Fluid losses in our third case were suspected to be over 20 L. In cases of delayed diagnosis, dehydration may be severe enough to precipitate hypovolemic shock, as observed in one of our patients. Early diagnosis and adequate intervention for diabetes prevent poor outcomes. The majority of children diagnosed with T2D showed neither symptoms of severe hyperglycemia nor ketosis at the time of diagnosis. Thus, these patients were identified through a urine glucose screening program conducted at school (14). However, obese patients with T2D might be associated with more severe insulin resistance and poorer glycemic control

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that accompany complications (15). It is important to be aware that early detection and proper diagnosis reduce complications, especially in obese patients with T2D. Childhood obesity has emerged as an important public health problem worldwide, and obesity is believed to promote T2D. Children with obesity face a four-fold higher risk of developing T2D (16). About one-third of the children and adolescents in the United States are overweight or obese (17), and the COVID19 pandemic has aggravated childhood obesity. The closure of schools has resulted in a decrease in physical activity, an increase in sedentary lifestyle behaviors and screen time, and more freedom to consume high-sugar and high-fat diets than before (18). In approximately 50% of adolescents, opportunities for physical activity were reduced during the COVID19 pandemic. Adolescents who did less physical activity were more likely to be overweight (odds ratio = 1.8) or obese (odds ratio = 2.2) (19). Obesity and physical inactivity lead to insulin resistance, and when combined with a genetic predisposition, can lead to T2D. We encountered three cases during the COVID19 pandemic in 2021. At this time, cases of mixed HHS and DKA are expected to occur more frequently and seriously than before.

Severe hypernatremia is a rare presentation of mixed DKA and HHS. Consumption of large amounts of carbohydrate-rich beverages appears to precipitate more severe metabolic derangement in mixed DKA and HHS. Clinicians need to be alert in identifying this increasingly common condition and should consider the impact that lifestyle factors can have on this potentially life-threatening condition.

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