Hyperglycemic hyperosmolar state in children: a case series

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ABSTRACT

Background: Hyperglycemic hyperosmolar state (HHS) is a life-threatening rare acute complication of diabetes mellitus (DM). The condition should be distinguished from diabetic ketoacidosis (DKA) as the management differs significantly. HHS is classically associated with type 2 DM, but it has been increasingly reported in type 1 DM as well. The literature regarding HHS in children is still sparse. The management of HHS in children is extrapolated from the adult study.

Cases: The first case was male 5 years old, and the second case was female 15 years old. Both cases were typed 1 DM patient. The first case was newly diagnosed. Both of the patients came with general weakness, mild dehydration, overly high blood sugar, normal blood pH, hypocalcemia, glucosuria and only mild ketonuria. In the second case develop, both patients were rehydrated, given insulin and discharged in 7-10 days without any sequela.

Conclusion: These case series emphasize the importance of recognizing HHS and differ it from DKA. These two cases prove that HHS is increasingly reported in children with clinical symptoms resembling DKA. It is also proven that with early diagnosis and correct management, children with HHS can be discharged home without any sequela.

Keywords: children, hyperglycemic hyperosmolar state, type 1 diabetes mellitus.


INTRODUCTION

Hyperglycemic hyperosmolar state (HHS) or previously known as hyperosmolar hyperglycemic non-ketotic coma (HONK), is a life-threatening rare acute complication of diabetes mellitus (DM). HHS is one of two hyperglycemic crises. The condition should be distinguished from diabetic ketoacidosis (DKA) as the management differs significantly. HHS is characterized by the triad of hyperglycemia (typically > 600 mg/dL), hyperosmolality (serum osmolality > 330 mOsm/L), and a mild metabolic acidosis (pH > 7.2). In DKA, there is hyperglycemia with ketonemia and acidosis. HHS is classically associated with type 2 DM, but it has been increasingly reported in type 1 DM as well. It portends a poorer prognosis than DKA, with mortality rates of between 10-35% in children. The literature regarding HHS in children is still sparse. There is no current standardized treatment guideline despite of increasing incidence in children. The management of HHS in children is extrapolated from the adult study.¹²

Hyperglycemic hyperosmolar state (HHS) is becoming more common in childhood, and optimal outcomes require a good understanding of the condition. Here we report two cases of the pediatric patient with hyperglycemic hyperosmolar states.

CASE I

A previously healthy 5-year-old male patient was referred to the emergency department with polyuria, polydipsia and weight loss in the last 2 months. He urinates around 10 times in the daytime and four times at night. Daily water intake is around 3 liters a day. The patient was also said to be progressively weak two days before admission after flying a kite the whole day under the sun. The patient lost 2 kilograms in 2 months despite of increased appetite. He likes to eat ice cream daily, drink chocolate milk boxes up to a liter a day and snacks up to 5 packs a day. History of fever, recent infection, dyspnea, nausea or vomiting were denied. The patient had no history of obesity. There was no family history of type 1 or type 2 DM.

Upon presentation, the patient was alert and able to communicate. Vital signs were as follows: blood pressure 90/60 mmHg, heart rate 90 beats per minute, respiratory rate was regular 30 times per minute, temperature 36.5°C with oxygen saturation 99% room air. Mild dehydration signs were noticed, such as sunken eyes and dry oral mucous but with normal skin turgor and capillary refill time. No signs of infection were found in the physical examination. The anthropometric evaluation revealed moderate protein energy malnutrition (weight 15 kg, height 112 cm, weight for length -3 to -2 SD, lower segment height 51 cm, upper segment/ lower segment ratio 1.2, arm span 111 cm, mid parental height 175.5 cm and genetic potential height 167-184 cm). His current height was within his genetic potential. Puberty status was Tanner stage 1.

Complete blood count result on the day of admission showed no significant result. Serum blood glucose revealed 695 mg/dL at presentation in the previous hospital and dropped to 321 mg/dL in our center. Urinalysis was done on the day of
admission with glucose +4 and ketone +1. HbA1c was 14.0% with C peptide 0.34 ng/mL. Anorganic phosphor was 3.89 mg/dL, magnesium was 1.60 mg/dL, blood urea nitrogen (BUN) was 7.6 mg/dL and creatinine was 0.60 mg/dL (glomerular filtration rate or GFR at 102 mL/minute/1.73 m2). Periodic arterial blood gas analysis and electrolyte count are shown in Table 1. The patient was then diagnosed with a hyperglycemic hyperosmolar state with mild dehydration, diabetes mellitus type I and moderate protein energy malnutrition.

The patient was given half intravenous maintenance fluid initially in the previous hospital and was continued with intravenous maintenance fluid with the addition of rehydration fluid for mild dehydration (3%) for a total of 48 hours. Nothing per oral was initiated. After 48 hours of fasting, the patient was given solid food (60% carbohydrate, 15% protein and 25% lipid). The patient was given an insulin drip of 0.1 unit/kg/hour in the previous hospital and was stopped in our emergency room. The insulin basal-bolus regimen was then administered after 48 hours of admission with an initial dose of 0.5 units/kg/day. The ratio of insulin and carbohydrate was 1:42. The insulin dose and timing were adjusted based on the blood sugar result to achieve glycemic control (Figure 1). The patient was discharged home after 7 days of admission. He did not develop any sequelae and was then given insulin basal (40%) bolus (60%) regimen dosage of 1.5 units/kg/day.

**CASE II**

Fifteen years old female was admitted to the emergency department with a chief complaint of generalized weakness followed by a decrease of consciousness since one hour before admission. There has been a history of type 1 DM since she was 4 years old. The patient never did a routine check-up to the hospital for her condition and was continued with insulin therapy regularly twice a day by her parents. The last insulin injection was in the morning before admission. There was no complaint of shortness of breath, fever, cough or runny nose. The patient only vomited once with a volume of approximately 100 ml with food and beverage in it. The last urination was 30 minutes before admission.

The patient likes to drink soda. There is a family history of diabetes mellitus in the grandmother and sibling of the patient. Upon presentation, the patient was somnolent (Glasgow coma scale E3V3M5) with blood pressure 110/80 mmHg, heart rate 119 times/minute, respiratory rate 18 times/minute, temperature 36.6°C and oxygen saturation of 99% in room air. From the physical examination, there was an obvious sign of mild dehydration, such as sunken eyes and a decrease in skin turgor. No signs of infection were found in the physical examination. The anthropometric evaluation revealed severe protein energy malnutrition (weight 26 kg, height 144 cm, BMI 12.56 kg/m2, BMI for age <-3 SD, lower segment height 75 cm,
upper segment/lower segment ratio 0.92, arm span 145 cm, mid parental height 153 cm and potential genetic height 144.5-161.5 cm) with clinical evidence of thin hair, old-man face, prominent ribs and baggy pants. Her current height was still within her genetic potential. Puberty status was Tanner stage 2.

Laboratory result on day 1 revealed Hb 11.4 g/dL, platelet 492 x 103/μL and random blood glucose 1162 mg/dL. Serum creatinine was 1.4 mg/dL, blood ureum nitrogen was 31.18 mg/dL with GFR at 72 mL/minute/1.73 m2. Liver function tests were within the normal limit. Urinalysis was done and revealed glucose +4 and ketone +2. HbA1c revealed 14% and C-peptide revealed 0.02 ng/mL. Periodic arterial blood gas analysis and electrolyte count are shown in Table 2. The patient was then diagnosed with hyperglycemic hyperosmolar state with mild dehydration, diabetes mellitus type I, Acute Kidney Injury stage injury pre-renal cause, delirium caused by metabolic and severe protein energy malnutrition marasmic type fifth condition in the rehabilitation phase.

The patient was admitted to PICU and given intravenous maintenance fluid with the addition of rehydration fluid for mild dehydration for a total of 48 hours, then continued with fluid requirement 1.5 times maintenance until acute kidney injury resolved (GFR at 132 mL/minute/1.73 m2 on June 16th, 2021). Intravenous potassium was given, and insulin drip was given with a rate of 0.1 units/kg/hour almost immediately. Blood sugar was initially monitored every hour, and blood gas analysis and electrolytes were monitored every four hours. Nothing per oral was initiated. The patient was started on a liquid diet after 24 hours of fasting. The insulin drip was stopped after 48 hours and switched to subcutaneous injection starting from 1 unit/kg/day divided into 2 doses (Figure 2). Vitamin A, vitamin B complex, vitamin C, folic acid, zinc and oral amoxicillin were administered due to severe protein energy malnutrition state. The patient was also given haloperidol 0.25 mg every 24 hours. The patient was discharged after 10 days with an insulin basal-bolus regimen of 1 unit/kg/day.

**DISCUSSION**

A hyperglycemic hyperosmolar state is a presentation of severe decompensation in a diabetic patient. It is more commonly reported in adults, but the incidence in children is rising. The first report of HHS on a child was in 1966. The population rate for HHS diagnoses in children aged 0-18 years old was 2.1 per 100,000 children in 1997, rising to 3.2 in 2009 and is related to rising rates of diabetes and obesity. The increased number of reported cases in children is most likely due to a steady rise
in type 2 diabetes mellitus and maturity-onset diabetes of the young (MODY), accounting for only 1-3% of cases of diabetes. In monogenic diabetes, there are no autoantibodies, and mutated gene is identified from genetic testing, which is inherited with an autosomal dominant pattern. In mitochondrial disorder, the function of mitochondria is impaired, which can affect pancreatic insulin production. In lipodystrophy patients, the fat builds up in places like the blood and internal organs, which can later cause diabetes and fatty liver disease. A family history of diabetes mellitus in the family must be assessed.\(^5\)\(^6\) In this case, there is no family history of diabetes mellitus in the first case, but there is a family history of diabetes mellitus in the grandmother and sibling of the patient in the second case.

There was a substantial percentage of HHS hospitalization reported among children with type 1 diabetes mellitus, which stood for 70.5% in one study in the United States.\(^7\) In this case, both of the patients have type 1 diabetes mellitus. In the first case, HHS was the presenting symptoms of type 1 diabetes mellitus. Genetic testing was not done in both patients, so monogenic diabetes still could not be fully excluded, especially in the first case whose family history is present. According to International Society for Pediatric and Adolescent Diabetes, the criteria for hyperglycemic hyperosmolar state (HHS), include plasma glucose concentration > 33.3 mmol/L (>600 mg/dL), venous pH > 7.25, arterial pH > 7.3, serum bicarbonate > 15 mmol/L, small ketonuria, absent to mild ketonuria, effective serum osmolality > 320 mOsm/kg, altered consciousness or seizure.\(^4\)

In this case, both cases reported is diabetes mellitus type 1 patient coming with generalized weakness. Both cases met the criteria for HHS except for effective serum osmolality, in which case I had effective serum osmolality of 299 mOsm/kg, and case 2 had effective serum osmolality of 301 mOsm/kg. This phenomenon can be explained by the administration of intravenous fluids at referring hospital prior to transfer to our emergency department. Serum osmolality of both cases was undoubtedly still high above the normal value.

Diagnosis delays are common in pediatric HHS caused by non-specific symptoms that also mimic diabetic ketoacidosis. In fact, HHS and diabetic ketoacidosis often fall on a continuum, and patients can present with a mixture of both conditions.\(^5\)\(^6\) In this case, both of the patients were followed long enough without any continuation to diabetic ketoacidosis. In HHS, the goal therapy of fluid resuscitation is to expand intra and extravascular volume, restore normal renal perfusion and promote a gradual decline in corrected serum sodium concentration and serum osmolality. The degree of dehydration in HHS is much greater than DKA, mostly twice of DKA, therefore requiring more aggressive fluid resuscitation with an initial recommendation of 20 mL/kg isotonic saline until adequate peripheral perfusion is established, followed by replacement of 12-15% fluid deficit over 24-48 hours. This fluid will be hypotonic in these patients. The main difference in management between HHS and DKA is urinary loss replacement in HHS patients with 0.45% saline. Inadequate fluid resuscitation is associated with an increased risk of complications in HHS. The target of fluid resuscitation is to decrease serum glucose concentration by 75-100 mg/dL per hour. Based on ISPAD recommendation, insulin administration begins at a dose of 0.025 to 0.05 U/kg/hour once the plasma glucose is decreasing less than 50 mg/dL per hour with fluid alone. Insulin therapy is not as vital early in treatment as in DKA, given the relative lack of ketosis in HHS. After administration of insulin, the dosage should be titrated until the decrease of blood glucose reaches 75-100 mg/dL/hour.\(^3\)\(^4\)\(^5\)\(^6\) In this case, both of the patients received intravenous fluid with correction of dehydration. Both of the patients responded well to the fluid therapy with an improvement in dehydration status even though the fluid administration was based on diabetic ketoacidosis standardized treatment. This might be explained by prior administration of fluid in referring hospital to the patient in the first case and non-severe degree of dehydration in the second case. Both of the patients received insulin therapy almost immediately at the first encounter of blood sugar higher than 600 mg/dL. Blood sugar significantly dropped in both patients afterward. No record of hypoglycemia in both patients, even with early insulin administration.

Another concerning condition in HHS is electrolyte imbalance. Children with HHS might develop hypernatremic dehydration, extreme potassium deficit, and decreased concentration of phosphate and magnesium. The goal for sodium concentration while commencing fluid resuscitation is a declining rate of 0.5 mmol/L/hour. Potassium replacement (40 mmol/L of replacement fluid) should begin as soon as serum potassium concentration is within the normal range and adequate renal function has been established. Serum hypophosphatemia may lead to rhabdomyolysis, hemolytic uremia, muscle weakness and paralysis. The mixture of potassium phosphate and potassium chloride or potassium acetate with a ratio of 50:50 generally permits adequate phosphate replacement while avoiding clinically significant hypocalcemia. Magnesium deficit in children with HHS should be corrected only in patients who experience severe hypomagnesemia and hypocalcemia during therapy. The recommended dose is 25-50 mg/kg/dose for 3-4 doses given every 4-6 hours with a maximum infusion rate of 150 mg/min and 2 grams/hour. Monitoring of electrolytes should be done every 2-3 hours, along with ECG monitoring.\(^4\)\(^11\)\(^12\) In this case,
both of the patients were screened for electrolyte imbalance and were monitored regularly. Only the second case received potassium therapy simultaneously with insulin administration, with the lowest potassium level being 3.15 mmol/L. Both of the patients developed asymptomatic hypocalcemia, and both did not receive any treatment.

Complications of HHS include a higher rate of venous thrombosis in the usage of the central venous catheter, malignant hyperthermia and rhabdomyolysis leading to acute kidney failure, severe hyperkalemia, hypocalcemia and muscle swelling causing compartment state. Delay in diagnosis is common, and morbidity and mortality in pediatric HHS are significant. Patients initially presenting with HHS may be at risk for serious complications from both DKA such as cerebral edema and HHS, such as hyperthermia, rhabdomyolysis and acute renal failure. Therefore, mandating close monitoring of mental status, body temperature, circulatory status and fluid-electrolyte balance.7-10 In this case, both of the patients were discharged without any sequelae. The only side effect we found is asymptomatic hypocalcemia that did not need any further treatment. Evidence found that hypocalcemia is a common condition in diabetes mellitus patients. It can be caused by a relative hypoparathyroidism state in diabetes mellitus patients leading to impaired calcium and phosphate regulation.11 The main focus was to educate the family and patient to control the blood sugar to prevent a future episode of either diabetic ketoacidosis or HHS.

CONCLUSION
These case series emphasize the importance of recognizing HHS and differ it from diabetic ketoacidosis because of its very different management. These two cases prove that hyperglycemic hyperosmolar state is increasingly reported in children with clinical symptoms resembling diabetic ketoacidosis. It is also proven that with early diagnosis and correct management, children with HHS can be discharged home without any sequelae.

CONFLICT OF INTEREST
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The authors are contributed to the writing of this research report, from the stage of proposal preparation, data collection and analysis to the preparation of reports in the form of publications.

REFERENCES