Abstract:
Altered mental status is an emergency that significantly contributes to morbidity and mortality in children, and thus, requires rapid and thorough evaluation. Identification of the underlying cause of altered mental status is crucial for appropriate clinical management. With a presentation of hyperglycemia and a family history of diabetes mellitus type 2, an astute physician would consider metabolic encephalopathy as the cause of altered mental status. We describe a critical case of altered mental status in a 14-year-old obese male adolescent with no history of chronic illness or surgeries who presented to the emergency department with hyperglycemia.

Keywords:
Altered mental status; hyperglycemia; hyperglycemia hyperosmolar syndrome; diabetic ketoacidosis

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Unresponsive: A Case of Hyperglycemia and Altered Mental Status

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A 14-year-old male adolescent presented to the emergency department (ED) with altered mental status. He was in his usual state of health until 2 days prior to presentation when his father noticed that he began to seem more fatigued and drowsier than usual and complained of a sore throat. His father thought the patient's change in affect was due to a possible viral infection. The fatigue continued and on the night prior to presentation, he began complaining of abdominal pain and his father reported several episodes of non-bloody, non-bilious emesis. The following morning, his father found him unresponsive in his room with no evidence of bowel or bladder incontinence. His father called 911 and emergency medical services (EMS) arrived at the house. EMS reported pinpoint pupils on exam and administered a dose of naloxone, but there was no improvement in mental status. A point of care serum glucose was too high to register on the prehospital glucometer. The patient was brought to the ED for further evaluation.

The patient's father reported that the patient had polyuria and polydipsia over the past year. The patient had a varied diet, but drank mostly soda and water. He reportedly woke up three or four times per night to urinate. His father denied noticing any weight loss. The patient's father could not recall all medications at home, but stated that there were no narcotics and all medications were kept locked

away. On the day that the patient first complained of fatigue, his father reported having cleared the sink drain with chemicals that resulted in the formation of a gas that caused everyone in the house to cough and complain of headaches. The patient subsequently left the house until the gas cleared.

The patient had a history of attention deficit hyperactivity disorder (ADHD) but no previous hospitalizations or surgeries and did not take any medications. He last saw his primary care physician 6 months prior to admission and had never been tested for diabetes mellitus. He was allergic to penicillin but did not have any other known allergies to medications or food. His immunizations were reportedly up-to-date.

He lived at home with his sister and father. His mother lived in a different state and was reportedly not involved in his life. Her family history was unknown. His father had a history of rheumatoid arthritis and there was a family history of diabetes mellitus type 2 on this side of the family: paternal grandmother, great-grandmother, and uncle all had diabetes mellitus type 2 though his father was unsure of age of onset or treatment of the condition. There was no history of type 1 diabetes or any other chronic diseases in the family.

On presentation to the ED, the patient's vital signs were as follows: temperature 97.2°F, heart rate 123 beat/min, respiratory rate 33 breaths per minute, and blood pressure 115/43 mmHg. The oxygen saturation was 99% on room air. He weighed 75 kg (99th percentile for age), and his height was 165.1 cm (49th percentile for age). His BMI was 33 kg/m^2 (99th percentile for age), categorizing him as obese based on Centers for Disease Control and Prevention guidelines. On physical examination, the patient appeared well-developed and well-nourished but was minimally responsive. His head, ears, and neck exam were within normal limits. Pupils were 1 to 2 mm in size and minimally reactive to light. Mucous membranes were dry. On cardiac examination, he was noted to be tachycardic with a regular rhythm without friction rub or murmurs. Pulmonary examination revealed tachypnea with Kussmaul breathing. There were no wheezes or rales on auscultation. The abdomen was soft, non-tender, and non-distended. His extremities were warm and dry. He was not diaphoretic. Neurologically, the patient presented with altered mental status and occasionally moaned, but did not respond to his name. There was occasional movement of his upper extremities in response to noxious stimuli. His Glasgow Coma Scale (GCS) score was 8.

Preliminary laboratory data in the ED revealed a white blood cell count of 22 240/mm^3, with 77.1% neutrophils, 11.7% monocytes and 9% lymphocytes. His hemoglobin was elevated at 16.2 g/dL as were his hematocrit at 58.4% and mean corpuscular volume (MCV) at 102.1 fL. Platelets were within normal limits at 232000/mm^3. A venous blood gas had a pH 7.04, pCO_2 of 42 mmHg, pO_2 of 48 mmHg, and bicarbonate of 11 mmol/L. A urinalysis revealed 1+ protein, glucose >500 mg/dL, 58 white blood cells/μL, trace leukocyte esterase, small ketones, and many bacteria. Urine toxicology was negative for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, codeine/morphine, cannabinoids, methadone, and oxycodone/oxymorphone. Point of care glucose was >600 mg/dL. Due to his altered mental status, a computed tomography (CT) scan of his head was obtained and revealed no evidence of acute herniation, intracranial hemorrhage, intracranial mass, edema, or ischemia.

Because his GCS score was 8 with pinpoint minimally reactive pupils, he was given a second dose of naloxone in our ED with minimal response. It was presumed the patient was in in diabetic ketoacidosis (DKA) and to treat him accordingly. Following this protocol, he was given two 1-L normal saline boluses and started on an insulin infusion at 0.1 U/kg per hour. He was admitted to the pediatric intensive care unit (PICU) for further management after an hour of care in the ED.

DISCUSSION

Altered mental status is an emergency that significantly contributes to morbidity and mortality in the pediatric population.[1] Causes of altered mental status can be classified as traumatic or nontraumatic, occurring at the same rate of 30 per 100 000 children per year.[1] Given that the patient had no signs of traumatic brain injury based on the CT and an atraumatic physical exam, the cause of his altered mental status was determined to be nontraumatic. Due to the wide range of etiologies, altered mental status poses a diagnostic challenge to medical professionals.[1,2] These etiologies include infections, poisoning and overdoses, metabolic disorders, seizures, drowning, intracranial masses or hemorrhages or hypoxic–ischemic injury resulting from one of the aforementioned mechanisms, or cardiopulmonary arrest.[1-4] As a result, early identification of the underlying cause of altered mental status is crucial for patient management. Evaluation must therefore be rapid, but thorough.

Research has revealed that infection is the most common cause of altered mental status in children, contributing to 30% to as much as 60% of cases.[1,2,4] Potential causes of central nervous system infection include bacterial, viral, fungal, and tubercular

meningitides and encephalitis.[1,4] Meningitis was excluded from the differential diagnosis of this patient due to lack of nuchal rigidity, seizures, or evidence of increased intracranial pressure.[5] In children, encephalitis commonly manifests with fever, seizures, focal neurologic signs, decreased consciousness, psychiatric symptoms, emotional lability, or movement disorders.[6,7] As the patient was afebrile and the family denied any acute behavioral or mental status changes, his clinical presentation was less likely to be consistent with a diagnosis of encephalitis. Other etiologies considered included ingestion and seizures. These were excluded given a negative toxicology screen for drugs of abuse and an abnormal and diffusely slow electroencephalogram (EEG) that ruled out epileptiform activity and non-convulsive status epilepticus as causes of the patient's altered mental status.

Given the patient's hyperglycemia and history of polydipsia and polyuria in the setting of his family history of type 2 diabetes, metabolic disorders causing encephalopathy were strongly considered. The patient's symptoms of nausea, vomiting, abdominal pain, and Kussmaul breathing support a diagnosis of diabetic ketoacidosis (DKA). DKA occurs most commonly in children with type 1 diabetes, but can occasionally occur in children with type 2 diabetes.[8,9] Although less common in children,[10] it is important to also consider hyperglycemic hyperosmolar syndrome (HHS) when diagnosing altered mental status in the setting of elevated glucose levels and a family history of type 2 diabetes. Both HHS and DKA are characterized by extreme elevations in serum glucose concentrations, but HHS differs in that it typically presents as hyperosmolality without ketosis[10] while DKA is characterized by metabolic acidosis with ketosis.[11,12] Additionally, a greater degree of dehydration is also evident in HHS relative to DKA.[10] Table 1 gives a summary of the typical laboratory features of HHS and DKA.

Recent evidence suggests that the incidence of HHS may be increasing in children due to increasing rates of both obesity and type 2 diabetes.[10,13-16] HHS can be difficult to distinguish from DKA in the acute setting and consequently, is often underdiagnosed in pediatric patients.[14] HHS and DKA are often considered on a spectrum with significant overlap of the conditions in the middle of the spectrum.[17] This further complicates the ability to distinguish between the diagnoses as two separate entities. For instance, some pediatric patients with DKA can present with hyperosmolality.[10] Nonetheless, HHS should be considered in a differential diagnosis for a presentation of serum glucose >600 mg/dl and serum osmolality >330 mOsm/L in the absence of significant ketosis and acidosis.[10]

TABLE 1. Laboratory characteristics and clinical signs associated with DKA and HHS.

Features of HHS and DKA		
	HHS	**DKA**
Hyperglycemia	++	+
Urine glucose	++	+
Urine ketones	−	+
Acidosis	−	+
Anion gap	+/−	+
Effective serum osmolality	+	+/−
Serum ketones	−	+
Dehydration	++	+
Kussmaul respiration	−	+
Alteration in mental status	+	+/−

Although the treatment of DKA is familiar to most physicians, the management of HHS in pediatric patients is not as well-known,[10] resulting in the implementation of DKA treatment protocols in patients with HHS. However, given the differences in pathophysiology, different therapeutic approaches are required for these conditions. Furthermore, distinguishing between HHS and DKA early is crucial. The symptoms associated with HHS gradually increase over time and may go unrecognized.[10] As a result, dehydration and electrolyte loss are more profound in HHS patients.[10] The dehydration associated with HHS is often masked because the hypertonicity in these patients preserves intravascular volume.[18] Initial treatment with IV fluid results in movement of water out of the intravascular space and osmotic diuresis may persist for hours.[10,19] During the initial course of treatment, these patients may suffer from large urinary fluid losses and thus, require more aggressive replacement of intravascular volume.[20,21]

HHS and DKA are both defined by states of hyperglycemia caused by resistance or deficiency of insulin secretion from the pancreas.[22] In contrast to DKA, HHS is a presentation of severe decompensation in the setting of a diabetic patient who typically retains some degree of insulin production, such as in a patient with type 2 diabetes mellitus.[18] This produces a state of hyperglycemia with minimal or no acidosis.[18] The clinical picture of HHS is further compounded by a disordered renal state. Typically, in cases of hyperglycemia, glycemic burden is alleviated through glucosuria. However, in a patient with HHS, there is decreased cationic exchange, which reduces electrolyte loss in the urine resulting

in unbalanced water loss.[18] HHS is characterized by higher hyperglycemia, associated osmotic diuresis and worsened dehydration relative to DKA.[22]

Treatment protocols further differ between the two conditions with regards to electrolyte replacement and insulin administration. When treating HHS, the rate of fluid replacement should be more rapid to prevent vascular collapse and subsequent mortality associated with HHS.[10,20,21] Patients in DKA historically have less aggressive fluid resuscitation due to the concern for cerebral edema; however, recent evidence suggests lower rates of mental status decline and brain injury in children with DKA who received rapid-rehydration therapy.[29] Because electrolyte deficits are more severe in HHS than DKA,[15] potassium replacement should be initiated as soon as potassium serum concentrations are within normal limits.[10,15,17] Additionally, early insulin administration is unnecessary in non-ketotic HHS and may actually increase mortality.[14] Insulin administration should only be considered when serum glucose concentration is not declining adequately with fluid administration alone.[10] Quick evaluation and diagnosis of HHS is crucial in implementation of therapeutic protocols that could be lifesaving in a patient with HHS.

CASE PROGRESSION

On admission to the PICU, the patient's glucose on a basic metabolic panel was 1845 mg/L with a low chloride of 92 mmol/L, elevated blood urea nitrogen (BUN) of 42 mg/dL, and elevated serum creatinine of 3.5 mg/dL. The patient's hemoglobin A1C was elevated at 15.4%. Given the degree of hyperglycemia, minimal ketonuria, and labs consistent with dehydration, a diagnosis of HHS was more likely. Thus, treatment for DKA was stopped and standard treatment for HHS was initiated with hydration with normal saline at 300–500 ml/hr. Insulin therapy was stopped and held until blood glucose (BG) was no longer declining. The patient's BG initially declined at a rate of 50–100 mg/dl per hour. However, it plateaued around 1000 mg/dl as his clinical status and kidney function deteriorated overnight. There was also a notable increase in his abdominal girth, which raised concern for extravasation. The patient became anuric overnight further explaining the non-improving hyperglycemia. He was briefly treated with dantrolene due to concern for a malignant hyperthermia-like process as a complication of HHS treatment after developing a fever of 102.7°F that rose to 107.9°F over 2 hours. He was afebrile after treatment later that evening. His insulin infusion was restarted at 3 AM the next morning at a dose of 0.025 U/kg per hour, but there was not much improvement of his glucose levels. His serum potassium was less than 2 mEq/L despite potassium supplementation. This likely indicated that the patient had been previously potassium depleted. The patient suffered from ventricular tachycardia and required cardioversion and subsequently received venoarterial extracorporeal membrane oxygenation (ECMO) cannulation. Continuous veno-venous hemofiltration (CVVH) was then initiated via ECMO for fluid removal.

The neurology service was consulted for altered mental status and concern for development of seizures. The patient's plasma osmolality was 372, which is associated with a high risk for seizures and cerebral edema. However, there were no clinical movements indicating the presence of seizures. Continuous EEG monitoring was initiated to rule out non-convulsive status epilepticus given his persistent altered mental status. The EEG was abnormal and diffusely slow with poor reactivity but did not reveal epileptiform activity.

The patient suffered from progressive hypotension, evidence of disseminated intravascular coagulation (DIC) with bleeding from the nasal and oral cavities, respiratory failure, central nervous system (CNS) failure, acute kidney injury, and abdominal compartment syndrome. His father requested withdrawal of support on his second day of admission. The cause of death was determined to be respiratory and central nervous system failure secondary to HHS. He passed away 36 hours after his initial presentation to the ED.

SUMMARY

Rapid and thorough evaluation of patients with altered mental status and low GCS is essential. DKA and HHS may initially present similarly, but ultimately, HHS can be distinguished by the absence of ketosis. Furthermore, treatment protocols differ for the two conditions and thus, early recognition of HHS is essential in guiding clinical decision making, providing appropriate care, and reducing the risk of morbidity and mortality.

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