

Subclinical cerebral edema in diabetic ketoacidosis in children

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Key Clinical Message

Subclinical cerebral edema in diabetic ketoacidosis tends to manifest with subtle neurological symptoms including headache, lethargy, or disorientation and a Glasgow Coma Scale of 14-15. Treatment of subclinical cerebral edema with hyperosmolar therapy for persistent symptoms is associated with good outcomes.

KEYWORDS

cerebral edema, diabetic ketoacidosis, pediatrics, subclinical cerebral edema

1 | INTRODUCTION

The incidence of childhood type I diabetes mellitus is increasing worldwide.¹ In 2011-2012, 17 900 children and adolescents in United States were diagnosed with new-onset type 1 diabetes.² Diabetic ketoacidosis (DKA) occurs in 25%-40% of these children and is the leading cause of hospitalizations, morbidity, and mortality.³⁻⁵ Cerebral edema is a serious complication of DKA. Clinically apparent cerebral edema (CEDKA) occurs in 1% of DKA children and is associated with devastating outcomes.^{5,6} Subclinical cerebral edema (SCE) occurs in more than half of DKA children.⁷⁻⁹ However, there are few reports that describe the clinical features and management of SCE.⁷⁻¹⁰ We report signs, symptoms, and treatment of SCE in DKA in two pediatric patients.

2 | CASE SERIES

2.1 | Case 1

A 8-year-old previously healthy girl presented with 2 weeks history of abdominal pain, emesis, polyuria, polydipsia, and 1-day history of lethargy and headache. Over the past 2 weeks, she had diffuse abdominal pain and intermittent episodes of

non-bloody, non-bilious vomiting associated with increased frequency of urination. Over the past day, she felt tired, and complained of generalized headache that brought her to the hospital. On arrival, her vital parameters revealed the following: temperature of 36.6°C; heart rate (HR): 136/min, blood pressure (BP): 123/73 mm Hg, respiratory rate (RR): 30/min, and oxygen saturation: 99%. Her physical examination revealed dry mucous membranes with capillary refill of 3-4 seconds, generalized tenderness of the abdomen, and Kussmaul pattern of breathing with clear breath sounds. Her neurological assessment revealed that she was lethargic. She answered questions and followed commands only on request. Her Glasgow Coma Scale (GCS) assessment was 14. Her initial laboratory studies revealed venous blood gas pH: 6.89, pCO₂: 20 mm Hg, HCO₃: 4 mmol/L; blood glucose: 494 mg/dL; serum chemistry: blood urea nitrogen (BUN): 10 mg/dL, serum creatinine: 0.77 mg/dL, serum sodium: 136 meq/L, serum potassium: 4.4 meq/L, and serum CO₂: <5 mmol/L. She was diagnosed with new-onset diabetic ketoacidosis. She received 10 mL/kg normal saline bolus and was commenced on 1.5 times maintenance intravenous fluids and 0.1 u/kg/h of continuous insulin infusion. There was no improvement of her neurological status in the next 2 hours and she continued to be lethargic and complain of headache. A concern for subclinical cerebral edema was raised. She was given 5 mL/

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kg of 3% hypertonic saline and within 2 hours of therapy, her lethargy improved and her headache subsided. Her GCS improved to 15. She was continued on intravenous fluids and insulin infusion for the next 22 hours that was transitioned to subcutaneous insulin. Her HbA_{1c} was 11.5% (102 mmol/mol). She was diagnosed to have new-onset type 1 diabetes mellitus. She was discharged home 4 days later with complete neurological recovery.

2.2 | Case 2

A 16-year-old female, a known patient with type 1 diabetes mellitus, depression, and bulimia presented with 2 days history of non-bloody and non-bilious vomiting and back pain. Her mother reported that over the past 1-2 weeks, her daughter was intentionally trying to have a high glucose level (>300 mg/dL) to reduce her body weight. On arrival, her vital parameters revealed the following: temperature of 36.3°C; HR: 138/min, BP: 154/97 mm Hg, RR: 39/min, and oxygen saturation: 96%. Her physical examination revealed dry mucous membranes with capillary refill of 2-3 seconds. She was tachypneic with Kussmaul pattern of breathing and clear breath sounds on auscultation. She complained of generalized headache. She was responsive to commands and answered questions appropriately. She would however, become agitated and disoriented intermittently. There were no focal neurological signs. Her GCS assessment was 14-15. Her initial laboratory studies revealed venous blood gas pH: 6.97, pCO₂: 21 mm Hg, HCO₃: 5 mmol/L; blood glucose: 596 mg/dL; serum chemistry: BUN: 23 mg/dL, serum creatinine: 0.7 mg/dL, serum sodium: 138 meq/L, serum potassium: 5 meq/L, serum CO₂: 6 mmol/L, and anion gap: 27. She was diagnosed with diabetic ketoacidosis. She received 20 mL/kg normal saline bolus and was commenced on 1.5 times maintenance intravenous fluids and 0.1 u/kg/h of continuous insulin infusion. There was no improvement of her neurological status in the next 2 hours and she continued to be disoriented, agitated, and complained of headache. A concern for subclinical cerebral edema was raised and 5 mL/kg of 3% hypertonic saline was administered. Her irritability improved and her headache subsided within 2 hours of therapy. Her GCS improved to 15. She was continued on intravenous fluids and insulin infusion for the next 18 hours that was transitioned to subcutaneous insulin. Her HbA_{1c} was 11.6% (103 mmol/mol). She was discharged home after 3 days of hospitalization with complete neurological recovery.

3 | DISCUSSION

Our case series demonstrate that SCE in children with DKA manifests with subtle neurological symptoms including headache, lethargy, or disorientation and a GCS score of

14-15. They do not demonstrate any focal neurological signs. Treatment with hyperosmolar therapy for persistent symptoms of SCE despite standard therapy causes resolution of their neurological symptoms with good outcomes.

Cerebral edema is a clinical diagnosis. CEDKA may occur in the absence of acute changes on head computed tomograms.^{6,11,12} Signs and symptoms of SCE are very subtle^{7,9,13} and can be easily missed. Hanas et al¹³ reviewed 292 patients in DKA over a 2-year period. A total of 16 patients were identified to have SCE based on symptoms of headache, vomiting, and lethargy. None of these patients had abnormal neurological signs and GCS score was not recorded.¹³ Krane et al⁹ evaluated six children in DKA for cranial computerized tomography scan early in their presentation. About 33% of these children with SCE had lethargy without any abnormal neurological signs. Their GCS score was not recorded.⁹ Glaser et al⁷ evaluated 48 children in DKA with magnetic resonance imaging during the course of their hospital admission. Lethargy with eye opening only in response to voice or pain (13 of the 15 children) and disorientation (nine of the 15 children) were the most frequent neurological symptoms in patients with SCE. Twelve of these 15 children had a GCS of 13-14. None of these children had any abnormal neurological signs. Marcin et al¹⁴ retrospectively evaluated 61 children with cerebral edema and DKA. Many patients did not have a GCS score recorded at the time of their neurological deterioration. They developed a 5-category neurological symptom score to correlate with GCS. All patients with lethargy or disorientation had a GCS equivalent of 11-15.¹⁴ Cerebral edema in DKA is a continuum with SCE representing an initial clinical manifestation. In our study, both patients with SCE had subtle neurological symptoms of headache, lethargy, and disorientation without any focal neurological signs and a GCS score of 14-15. These patients did not have any rapid deterioration of their neurological status, signs of cerebral herniation, or fulfill the diagnostic criteria recommended to diagnose CEDKA clinically.¹¹

There is an estimated 40%-90% mortality from CEDKA.^{5,12} About 15%-26% survivors of CEDKA are left with permanent neurological damage.⁴ The incidence of developing CEDKA has nearly doubled from 2002 to 2012.¹⁵ By the time CEDKA is diagnosed, cerebral edema may be severe enough to be associated with high morbidity and mortality.^{4,5,12} Treatment of SCE may help to mitigate this complication. However, treatment options of SCE reported in literature are sparse.^{7,9,13} Hanas et al¹³ treated two of their 16 SCE patients with mannitol and both recovered within 1-2 hours of therapy. In the study period of 1982-1997, Marcin et al¹⁴ treated most of their cerebral edema patients with GCS score between 11 and 15 with mannitol therapy. Treatment of cerebral edema in DKA with hyperosmolar agents is recommended as the pathophysiology of cerebral edema is not very well understood.^{6,16-19} An ischemic⁶ and/

or vasogenic¹⁸ process is proposed to play a role in the genesis of DKA related cerebral edema. The magnetic resonance studies of the brain in SCE (using quantification of the apparent diffusion coefficient) reveal vasogenic rather than cellular edema¹⁹ in whom hyperosmolar therapy may be beneficial. Based on neurosurgical and traumatic brain injury studies, the traditional therapy for CEDKA has been intravenous mannitol.¹² Over the past decade, the use of 3% hypertonic saline as the hyperosmolar agent for CEDKA in United States has increased fourfold and is now the preferred osmotherapy agent rather than mannitol.²⁰ There has been concern that the use of 3% hypertonic saline alone is associated with a higher mortality than mannitol in patients treated for CEDKA.²⁰ A scientific equipoise is currently recommended regarding the efficacy in the use of mannitol vs 3% hypertonic saline in the treatment of cerebral edema in DKA.²¹ In our study, both patients received 3% hypertonic saline and showed neurological recovery in the next 2 hours.

Limitations of our small case series include lack of neurological imaging studies in our patients of SCE. Cerebral edema on brain imaging, however, may not be detectable even in patients with CEDKA.^{6,11,12} Secondly, we chose to intervene and administer hyperosmolar therapy for SCE. It is possible that our patients would have complete neurological recovery without treatment.^{7,9,13} However, both of our patients with SCE did not show any clinical improvement in their neurological status over the next few hours following presentation. There was a concern that SCE would progress to CEDKA that is associated with poor outcomes.^{4,5,12} Lastly, altered mental status in DKA patients can be related to variety of other factors including sleep deprivation, severe acidosis, or neurological injury other than cerebral edema.¹¹ It would be unlikely to see any significant clinical recovery following administration of hyperosmolar therapy in our patients, if neurological abnormalities were related to these factors.

In summary, we conclude that detailed neurological assessment must be done in children presenting with DKA. SCE tends to manifest with subtle neurological symptoms including headache, lethargy, or disorientation and a GCS of 14-15. Treatment of persistent symptoms in SCE with hyperosmolar therapy should be considered as it is associated with good outcomes.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

HSA: was involved in patient management, and in preparation, review, and submission of the manuscript.

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